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Mission and Preface

USP 36–NF 31 and Supplements

This section provides background information on the United States Pharmacopeial Convention (USP), as well as general information about the 36th revision of the *United States Pharmacopeia* (USP 36) and the 31st edition of the *National Formulary* (NF 31) and their Supplements. Unless otherwise noted, the text in USP 36–NF 31 is official May 1, 2013, the text in the *First Supplement* to USP 36–NF 31 is official August 1, 2013, and the text in the *Second Supplement* to USP 36–NF 31 is official December 1, 2013.

MISSION STATEMENT

USP–NF is published in continuing pursuit of the mission of USP: *To improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and benefit of medicines and foods.*

HISTORY

On January 1, 1820, 11 physicians met in the Senate Chamber of the U.S. Capitol building to establish a pharmacopeia for the United States. These practitioners sought to create a compendium of the best and most fully established medicines, give them useful names, and provide recipes for their preparation. Nearly a year later, on December 15, 1820, the first edition of *The Pharmacopoeia of the United States* was published. Over time, the nature of the *United States Pharmacopeia* (USP) changed from being a compendium of recipes to a compendium of documentary standards for identity and quality that typically involve reference materials used as comparison standards in specified tests and assays. The publishing schedule of USP also changed over time. From 1820 to 1942, USP was published at 10-year intervals; from 1942 to 2000, at five-year intervals; and beginning in 2002, annually.

In 1888, the American Pharmaceutical Association published the first *National Formulary* under the title *The National Formulary of Unoficial [sic] Preparations* (NF). Both USP and NF were recognized in the Federal Food and Drugs Act of 1906 and again in the Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act). In 1975, USP acquired the *National Formulary* (NF), which now contains excipient standards that also call for reference materials. USP continues to develop USP and NF, through the work of the Council of Experts, into compendia that provide standards for articles based on advances in analytical and metrological science. As these and allied sciences evolve, so do USP and NF.

CONTENT OF USP–NF

USP–NF contains official substance (ingredient) and preparation (product) monographs for official articles recognized in USP–NF. The terms *official substance*, *official preparation*, and *official article* are defined in the *General Notices and Requirements* (General Notices). With few exceptions, all articles for which monographs are provided in USP–NF are legally

marketed in the United States or are contained in legally marketed articles.

A USP–NF monograph for an official substance or preparation may consist of various components, including the article's name; definition; packaging, storage, and other requirements; and a specification. The specification consists of a series of universal tests (description, identity/identification, impurities, assay) and specific tests, one or more analytical procedures for each test, and acceptance criteria. Ingredients are defined as either drug substances or excipients. An excipient is any component, other than the active substance(s), intentionally added to the formulation of a dosage form. Excipients are not necessarily inert. Drug substances and excipients may be synthetic, semi-synthetic, drawn from nature (natural source), or manufactured using recombinant technology. Drugs that consist of larger molecules and mixtures requiring a potency test are usually referred to as biologicals or biotechnological articles.

General chapters provide frequently cited procedures, sometimes with acceptance criteria, in order to compile into one location repetitive information that appears in many monographs. New and revised monographs and general chapters and obsolete matter deleted from this edition are indicated in the *Admissions* section.

USP–NF Organization—USP–NF is printed as a three-volume set. *Volume 1* includes front matter (*Mission and Preface*, *People*, *Governance* pages and websites, and *Admissions/Annotations*). It also includes *USP General Notices*, general chapters, dietary supplement general chapters, *Reagents*, *Reference Tables*, dietary supplement monographs, *NF Admissions/Annotations*, *Excipients*, and *NF monographs*. *Volume 2* includes USP monographs A–I, and *Volume 3* includes USP monographs J–Z. To facilitate convenient use and reference, all three volumes include the full index, as well as the *USP General Notices* and the *Guide to General Chapters*. General chapters specific to dietary supplements are included in numerical order with the rest of the general chapters in USP. Excipient monographs usually are presented in NF but also may appear in USP with suitable cross-referencing when they are also drug substances. The *Excipients* section (*Volume 1*) presents a tabulation of excipients by functional category.

Revisions to USP–NF—USP–NF is continuously revised. Revisions are presented annually as *Standard Revisions* in USP–NF and in twice-yearly *Supplements*, and as *Accelerated Revisions* on USP's website [Errata, Interim Revision Announcements (IRAs), and Revision Bulletins].

Standard Revisions—USP's Standard Revision Process calls for publication of a proposed revision in the *Pharmacopeial Forum* (PF) for a 90-day notice and comment period and, after the revision is approved by the relevant USP Expert Committee, publication in the next USP–NF or *Supplement*, as applicable.

Accelerated Revisions—The Accelerated Revision process is used to make revisions to USP–NF official more quickly than through USP's *Standard Revisions* process. Accelerated Revisions, which include *Errata*, *IRAs*, and *Revision Bulletins*, are posted on USP's website, do not always require notice and

comment, and allow for a revision to become official prior to the next USP–NF or Supplement. See the *USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF*, which is posted on USP’s website.

Errata—An Erratum/Errata is content erroneously published in a USP publication that does not accurately reflect the intended official or effective requirements as approved by the Council of Experts. These typically are changes that do not have a broad impact on the standards. Errata are not subject to public comment and are communicated to the stakeholders by posting in the “Official Text” section of USP’s website. As of USP 36–NF 31 errata will no longer be published in the USP–NF and Supplement print products. Errata become official on the first day of the month following their posting to the USP website. Errata are incorporated into the next available USP–NF or Supplement and are tagged when printed as described below.

Interim Revision Announcements (IRAs)—An IRA appears in PF first as a *Proposed Interim Revision Announcement* with a 90-day comment period. If there are no significant comments, the IRA becomes official in the “Official Text” section of USP’s website, with the official date indicated. IRAs are incorporated into the next available USP–NF or Supplement.

Revision Bulletins—If circumstances require rapid publication of official text, a revision or postponement may be published through a *Revision Bulletin*. *Revision Bulletins* are posted on USP’s website with the official date indicated. *Revision Bulletins* are incorporated into the next available USP–NF or Supplement.

Pharmacopeial Forum (PF)—The PF is USP’s official publication for public notice and comment. Proposals for revision are presented in the *In-Process Revision* or the *Proposed Interim Revision Announcement* (see above) sections and represent draft revisions that are expected to advance to official status pending final review and approval by the relevant Expert Committee.

On January 3, 2011, PF transitioned to an online-only publication that is available free of charge. The print version is no longer available. The new online-only PF includes proposed changes and additions to the USP–NF, including *Stage 4 Harmonization*, and *Stimuli* articles for which USP is seeking public comments. All proposals, including IRAs, will have a 90-day comment period. Other information that was contained in PF, including official text (final IRAs), is now published solely on USP’s website or moved into other USP publications.

This change to make PF freely available will help facilitate open and public participation when revisions are proposed to the USP–NF.

Supplements—Supplements to USP–NF follow a standard schedule each year: the *First Supplement* is published in February and becomes official August 1. The *Second Supplement* is published in June and becomes official December 1. Users of USP print products must retain Supplements and check the “Official Text” section of USP’s website in order to have up-to-date official text. The USP–NF online version is updated with each Supplement or annual revision. Each time a new edition or Supplement is released during the subscription period, a new electronic version is issued. The *Index* in each Supplement is cumulative and includes citations to the annual revision and, for the *Second Supplement*, citations to the *First Supplement*. The contents of the two Supplements are integrated into the annual edition of the following year, along with new official revisions that have been adopted since the *Second Supplement* to the previous compendia.

USP–NF Spanish Edition—In 2006, USP began providing a Spanish edition of USP–NF. Maintenance of this edition follows the same revision approaches as the English edition.

USP Reference Standards—When approved for use as a comparison standard as a component of a USP monograph or other compendial procedure, use of USP Reference Standards promotes uniform quality of drugs and supports reliability and consistency by those performing compliance test-

ing and other users of USP–NF, including manufacturers, buyers, and regulatory authorities. The *USP Catalog*, which lists the collection of USP Reference Standards, can be accessed on USP’s website (www.usp.org). The listing identifies new items, replacement lots, lots of a single item that are simultaneously official, lots deleted from official status, and a preview of items eventually to be adopted. Purchase order information is included, and the names of distributors who can facilitate international availability of these items are suggested. This program benefits from the widespread voluntary contribution of suitable materials and test data from pharmaceutical manufacturers. USP advances this material via careful characterization studies and collaborative testing, followed by review and approval of the compendial use of the reference material by Expert Committees of the Council of Experts.

Shading and Symbols—Shading is used to identify text that has been modified, added or deleted since it was last published. Symbols identify the beginning and end of each revision, or nonharmonized text. The following table summarizes the types of symbols and the associated subscripts used in USP publications:

Revision Type	Symbol	Subscript
Interim Revision Announcement	●new text● (IRA 1-Jul-2013)	(IRA 1-Jul-2013)*
Revision Bulletin	●new text● (RB 1-Jan-2013)	(RB 1-Jan-2013)*
Text deletion	● (IRA 1-Jul-2013) OR ■1S (USP36) OR ▲(USP36)	(IRA 1-Jul-2013)* 1S (USP36)* USP36**
Adopted in Supplement	■new text■1S (USP36)	1S or 2S (USP annual edition)*
Adopted in USP–NF	▲new text▲(USP36)	USP annual edition**
Harmonization	◆ indicates residual national text or nonharmonized text	
Errata	●new text● (ERR 1-Jul-2012)	(ERR 1-Jul-2012)

* A subscript number or date indicates the IRA, Revision Bulletin, or Supplement in which the revision first appeared.

** An example of a revision that was officially adopted in the USP–NF would be ▲(USP36).

The following table shows symbols and official dates for IRAs and Supplements to USP 36–NF 31.

IRAs and Supplements to USP 36–NF 31 Official Dates and Symbols			
Supplement	Proposed IRA	Official Date	Symbols
1	39(1)	July 1, 2013	●and● (IRA 1-Jul-2013)
		Aug. 1, 2013	■and■1S (USP36)
	39(2)	Sept. 1, 2013	●and● (IRA 1-Sep-2013)
2	39(3)	Nov. 1, 2013	●and● (IRA 1-Nov-2013)
		Dec. 1, 2013	■and■2S (USP36)
	39(4)	Jan. 1, 2014	●and● (IRA 1-Jan-2014)
	39(5)	Mar. 1, 2014	●and● (IRA 1-Mar-2014)
	39(6)	May 1, 2014	●and● (IRA 1-May-2014)

Commentary—In accordance with USP’s *Rules and Procedures of the Council of Experts*, USP publishes all proposed revisions to USP–NF for public review and comment in the PF, USP’s bimonthly online journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be republished in PF for further notice and comment, in accordance with the *Rules and Procedures*. In cases when proposals advance to official status without republication in PF, a summary of comments received and the appropriate Expert Committee’s responses

are published in the *Commentary* section of the USP website at the time the revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of the Expert Committee's response to public comments. If there is a difference between the contents of the *Commentary* and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary*, shall prevail.

Chemical Names and CAS Registry Numbers—Chemical subtitles given in the monographs are index names used by the Chemical Abstracts Service (CAS) of the American Chemical Society. They are provided only in monographs in which the titles specify substances that are definable chemical entities. The first subtitle is the inverted form of the systematic chemical name developed by CAS for the purpose of the Collective Index (CI). The second subtitle, given in uninverted form, is a preferred IUPAC name (PIN) sanctioned and used by the International Union of Pure and Applied Chemistry (IUPAC). Preferred IUPAC names are also used by the World Health Organization (WHO). Occasionally a third subtitle is supplied for historical reasons or when the synonym uses an alternative, but equivalent, naming convention. Monographs with chemical subtitles also generally carry CAS registry numbers. These bracketed numbers function independently of nomenclature as invariant numerical designators of unique, unambiguous chemical substances in the CAS registry and thus are convenient and widely used.

Print and Electronic Presentations—All USP–NF publications are available in print form (with the exception of the *Pharmacopeial Forum* and *Accelerated Revisions*, discussed above, which are posted on USP's website until incorporation into the next USP–NF or *Supplement*). In addition, USP–NF and its two annual *Supplements* are available in USB flash drive and online versions. The USB flash drive version makes USP–NF accessible to users on their computer hard drives. The online format allows individual registered users to access the online format through the Internet. Both electronic formats provide access to official USP–NF content, along with extensive search options. The electronic formats are cumulatively updated to integrate the content of *Supplements*. A searchable electronic version of the *USP Dictionary* also is available.

USP GOVERNING, STANDARDS-SETTING, AND ADVISORY BODIES

USP's governing, standards-setting, and advisory bodies include the USP Convention, the Board of Trustees, the Council of Experts and its Expert Committees, Expert Panels (formerly known as Advisory Panels), and staff. Additional volunteer bodies include Stakeholder Forums, Project Teams, and Advisory Groups, which act in an advisory capacity to provide input to USP's governing, standards-setting, and management bodies.

USP Convention—The composition of the USP Convention membership is designed to ensure a global representation from all sectors of health care, with an emphasis on practitioners, given USP's practitioner heritage (see the *History* section). Voting Delegates of Convention member organizations elect USP's President, Treasurer, other members of the Board of Trustees, and the Council of Experts. They also adopt resolutions to guide USP's strategic direction and amend USP's Bylaws. Convening on a 5-year cycle, the last meeting of the USP Convention occurred in April 2010 in Washington, DC. A listing of all current Voting Delegates of the USP Convention is included in the *People* section.

Board of Trustees—USP's Board of Trustees is responsible for the management of the business affairs, finances, and property of USP. During its 5-year term, the Board defines USP's strategic direction through its key policy and operational decisions. A listing of the members of the

2010–2015 Board of Trustees is included in the *People* section.

Council of Experts—The Council of Experts is the standards-setting body of USP. For the 2010–2015 cycle it is composed of 24 members, each of whom chairs an Expert Committee. Members of the Council of Experts were either elected to 5-year terms by USP's Convention or, for Chairs of Expert Committees created during the cycle, elected by the existing Council of Experts for the remainder of the cycle. These Chairs in turn elect the members of their Expert Committees. The Expert Committees are responsible for the content of USP's official and authorized publications (see *Figure 1*). The Executive Committee of the Council of Experts includes all Expert Committee Chairs and provides overall direction, is an appeals body, and performs other functions that support the Council of Experts' operations.

Expert Panels to the Council of Experts—The Chair of the Council of Experts may appoint Expert Panels to assist the Council of Experts by providing advisory recommendations to particular Expert Committees in response to a specific charge consistent with the Expert Committee's Work Plan. Expert Panels are continuously formed; their topics and membership appear in the *People* section.

Stakeholder Forums and Project Teams—USP has formed several domestic and international Stakeholder Forums and Project Teams to exchange information on USP's standards-setting activities. Stakeholder Forums may form Project Teams to work on selected topics. The following lists the current USP Stakeholder Forums.

North American Stakeholder Forums (United States and Canada)

- Prescription/Nonprescription
- Dietary Supplements
- Food Ingredients
- Veterinary Drugs

International Stakeholder Forums

- India
- Mexico
- Brazil
- Others

USP also conducts Science and Standards Symposia (formerly Annual Scientific Meetings) in the United States, India, China, Latin America, Middle East/North Africa, and other regions of the world.

Staff—USP maintains a staff of over 800 scientists, professionals, and administrative personnel at its Rockville, Maryland, headquarters and throughout the world, including an account management office in Basel, Switzerland, and laboratory facilities in Hyderabad, India; Shanghai, China; and São Paulo, Brazil.

RULES AND PROCEDURES

Governing Documents—USP–NF standards are recognized widely because they are authoritative and science-based and are established by a transparent and credible process. See the *Articles of Incorporation* section in this book; the *Bylaws* and the *Rules and Procedures of the Council of Experts* are available on USP's website (www.usp.org). Collectively, these documents serve USP volunteers and staff as the governing principles for USP's standards-setting activities.

Conflicts of Interest—USP's Conflict of Interest provisions require all members of the Council of Experts, its Expert Committees, Expert Panels, Board of Trustees, and key staff to disclose financial or other interests that may interfere with their duties as USP volunteers. Members of the Board of Trustees, Council of Experts, and its Expert Committees are required to serve USP as individual experts and not serve any outside interest, and are not allowed to take part in the final discussion or vote on any matter in which they have a conflict of interest or the appearance of a conflict of inter-

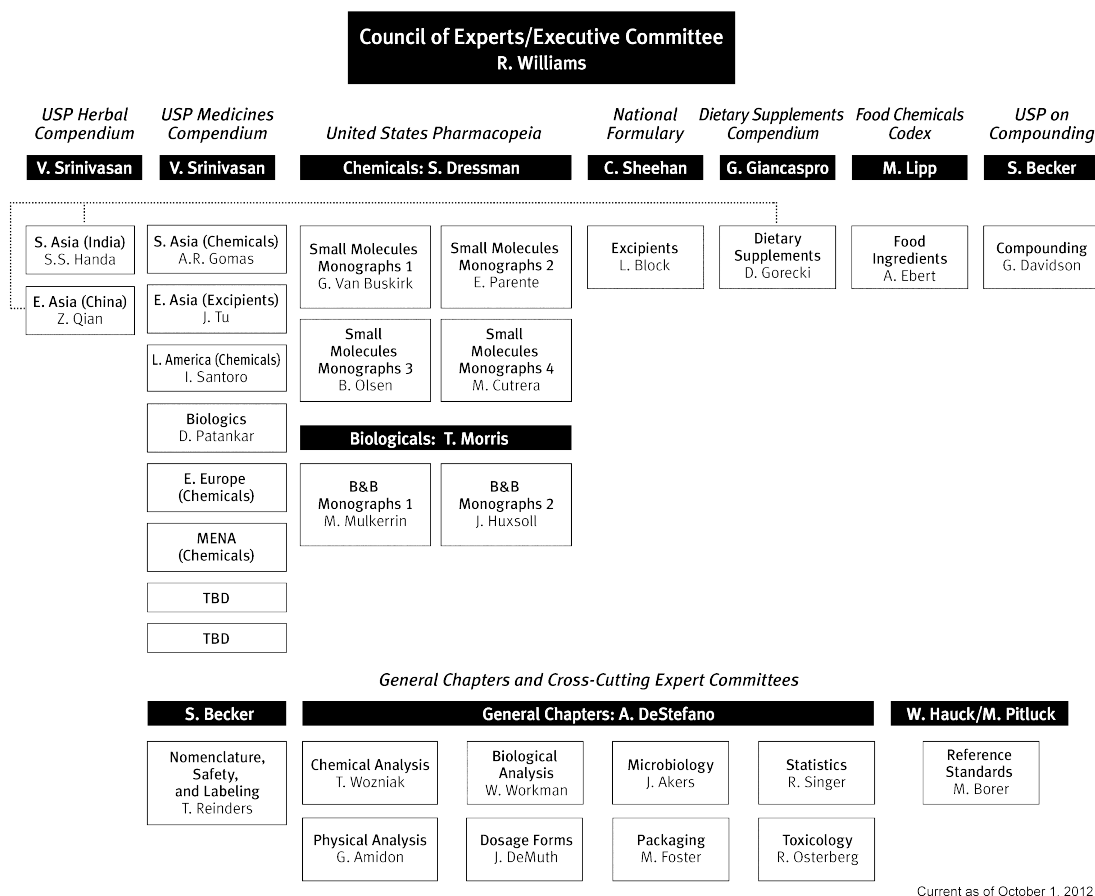


Figure 1. 2010–2015 USP Council of Experts.

est. Members of advisory Expert Panels may participate and vote, so long as any notable interests and conflicts have been adequately and promptly disclosed and are communicated to the relevant Expert Committee along with any Expert Panel recommendations.

Confidentiality and Document Disclosure—Members of the Council of Experts, Expert Committees, and Expert Panels sign confidentiality agreements, in keeping with USP's Confidentiality Policy and the confidentiality provisions of the *Rules and Procedures of the Council of Experts*. The USP Document Disclosure Policy, available on USP's website, contributes to the transparency of the standards-setting process by making information available to the public, yet provides protection to manufacturers and others who submit confidential information to USP.

Authority for Publication—USP–NF is published in accordance with Article II, Purposes, of the USP Bylaws, which states, "The purposes for which the Convention is formed are as set forth in the Articles of Incorporation and include developing and disseminating public standards for medicines and other articles, and engaging in related public health programs."

USP–NF REVISION PROCESS

Public Participation—Although USP's Council of Experts is the ultimate decision-making body for USP–NF standards, these standards are developed by an exceptional process of public involvement and substantial interaction between USP and its stakeholders, both domestically and internationally. Participation in the revision process results from the support

of many individuals and groups and also from scientific, technical, and trade organizations.

Requests for Revision of the USP–NF, whether new monographs or general chapters or those needing updating, contain information submitted voluntarily by manufacturers and other interested parties. At times USP staff and Expert Committees may develop information to support a *Request for Revision*. USP has prepared a document titled *Guideline for Submitting Requests for Revision to USP–NF* (available at www.usp.org; search on "Submission Guidelines"). Via PF, USP solicits and encourages public comment on these revision proposals. Comments received are considered by the Expert Committees, who determine whether changes should be made to the proposed revisions based on such comments. Proposed standards are finalized when Expert Committees vote to make them official text in USP–NF. Thus, the USP standards-setting process gives those who manufacture, regulate, and use therapeutic products the opportunity to comment on the development and revision of USP–NF standards. Figure 2 shows the public review and comment process and its relationship to standards development.

Working with the Food and Drug Administration (FDA)—As specified in U.S. law, USP works with the Secretary of the Department of Health and Human Services in many ways. The principal agency in the Department for this work is the Food and Drug Administration. The FDA Liaison Program allows FDA representatives to participate in Expert Committee and Expert Panel meetings, enabling interactions between FDA scientific staff and Expert Committees. Staff in the FDA Centers who are responsible for review of compendial activities provide specific links and opportunities for exchange of comments. Dr. Paul Seo in the Center for Drug Evaluation and Research provides a primary compendial point of contact between FDA and USP.

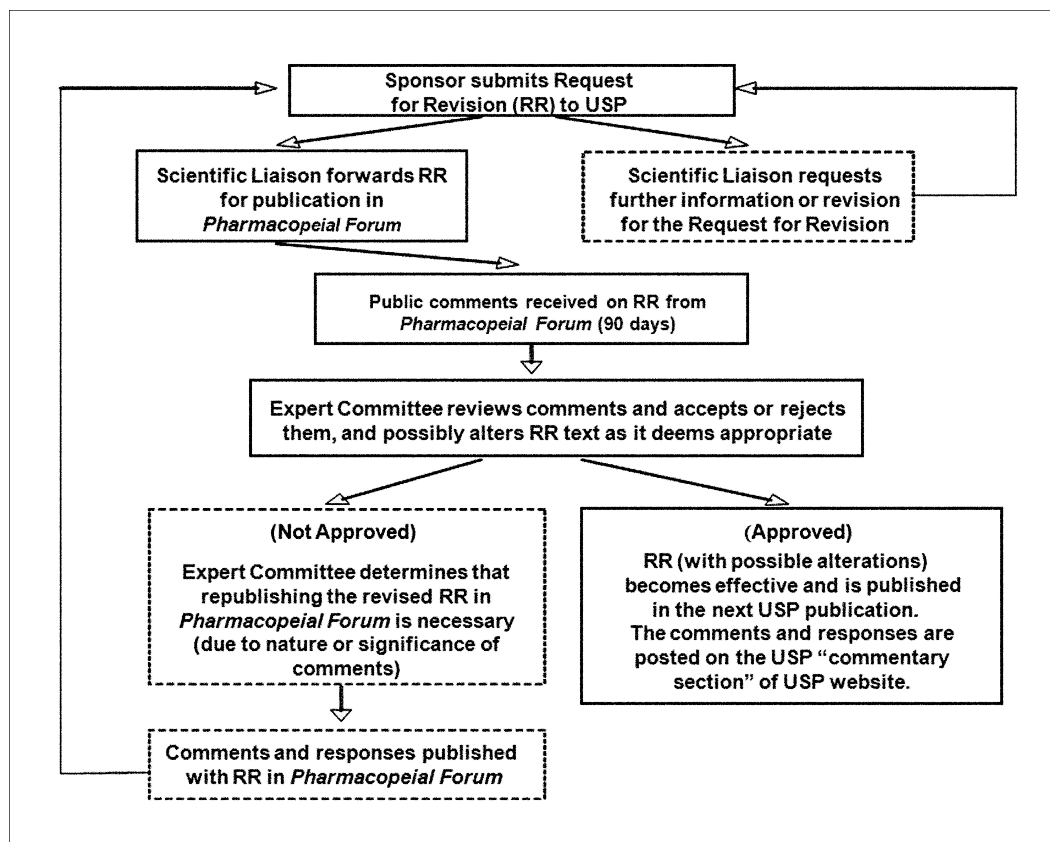


Figure 2. USP's standards-setting public review and comment process.

LEGAL RECOGNITION

Recognition of USP–NF—USP–NF is recognized by law and custom in many countries throughout the world. In the United States, the FD&C Act defines the term “official compendium” as the official USP, the official NF, the official *Homeopathic Pharmacopeia of the United States*, or any supplement to them. As noted below (and in *General Notices* section 2.30), USP–NF standards play a role in the adulteration and misbranding provisions of the FD&C Act (which apply as well to biologics, a subset of drugs, under the Public Health Service Act). USP has no role in enforcement of these or other provisions that recognize USP–NF standards, which is the responsibility of FDA and other government authorities in the United States and elsewhere.

Under the relevant FD&C Act provisions, a drug will be deemed misbranded unless its label bears to the exclusion of any other nonproprietary name the “established” name, which ordinarily is the compendial name (see discussion of *Nomenclature*, below). A drug with a name recognized in USP–NF must comply with the identity/identification requirements of its monograph, or be deemed adulterated, misbranded, or both. Drugs also must comply with compendial standards for strength, quality, and purity (tests for assay and impurities), unless labeled to show all respects in which the drugs differ. FDA requires that names for articles that are not official must be clearly distinguished and differentiated from any name recognized in an official compendium. Drugs with a name recognized in USP–NF also will be considered misbranded unless they meet compendial standards for packaging and labeling.

Drugs—USP's goal is to have substance and preparation (product) monographs in USP–NF for all FDA-approved drugs, including biologics, and their ingredients. USP also develops monographs for legally marketed therapeutic products not approved by FDA, e.g., pre-1938 drugs, over-the-

counter (OTC) drugs marketed under FDA's OTC Monograph system, dietary supplements, and compounded preparations. Although submission of information needed to develop a monograph by the Council of Experts is voluntary, compliance with a USP–NF monograph, if applicable, is mandatory.

Biologics—In the United States, all biologics are considered a subset of drugs, whether they are approved by FDA under the FD&C Act (and receive a new drug application [NDA]) or under the Public Health Service Act (PHS Act, where they receive a biologics license application [BLA]). As a result, all PHS Act biologics are subject to the drug regulatory requirements of the FD&C Act, which means they are required to comply with the adulteration and misbranding provisions of the FD&C Act, including USP–NF compendial requirements. This is equally so for biologics approved under the longstanding PHS Act “351(a)” pathway, as well as the new “351(k)” pathway for biosimilars added by the 2010 healthcare reform legislation (Biologics Price Competition and Innovation Act, Title VII, Subtitle A of the Patient Protection and Affordable Care Act, Public Law 111-148).

Medical Devices—Section 201(h) of the FD&C Act defines a device as an instrument, apparatus, similar article, or component thereof recognized in USP–NF. Section 502(e) of the FD&C Act defines the established name of a device in the absence of an FDA designation of the official name as the official title in an official compendium. Despite these statutory provisions, there is no comparable recognition of USP's role in establishing compendial standards for medical devices as exists for drugs and biologics. Under authority granted by the Food and Drug Administration Modernization Act of 1997, the Center for Devices and Radiological Health recognizes national and international standards, including some USP tests and assays, for medical devices.

Dietary Supplements—The Dietary Supplement Health and Education Act of 1994 amendments to the FD&C Act

provide that a dietary supplement may be deemed a misbranded food if it is covered by the specifications of an official compendium (e.g., *USP–NF*), is represented as conforming to the specifications of an official compendium, and fails to so conform. This contrasts with pharmaceutical products, wherein conformance to applicable compendial standards is mandatory, whether or not the product claims to conform.

Compounded Preparations—Compounding means the preparation, mixing, assembling, altering, packaging, and labeling of a drug or device or other article, as the result of a practitioner's order or in anticipation of such an order based on routine, regularly observed prescribing patterns. *USP* provides both general chapters and monographs for compounded preparations. Compounded preparation monographs include formulas (ingredients and quantities), specific directions to correctly compound the particular preparation, packaging and storage information, labeling information, pH, beyond-use dates based on stability studies, and detailed assays (majority of monographs). Standards in *USP–NF* for compounded preparations may be enforced by both the states (as pharmacy practice/compounding is traditionally regulated by state boards of pharmacy), and FDA (as compounded preparations subject to FDA regulation as drugs remain subject to the adulteration and misbranding provisions of the FD&C Act, which require conformance to *USP–NF* standards).

Nomenclature—*USP*, as a member of the United States Adopted Names (USAN) Council, works to determine names for drug and biological substances. *USP*'s authority to develop official nonproprietary names is identified in the misbranding provision of the FD&C Act, section 502(e) (see also FDA's policy on established names set forth in 21 CFR 299.4). Under both *USP* rules and applicable federal law, official names mean the official title of an article recognized in *USP* or *NF*, which is determined when a monograph for the article is published, including the article's name in the monograph title. *USP* Expert Committees may not complete work on an applicable monograph until after FDA has licensed a drug or biologic, or USAN has designated a name. FDA-approved nonproprietary names are considered by FDA and the courts to be interim names that exist only unless and until *USP* designates a name. Congress in 1962 gave FDA the authority to change a *USP*-designated name; in the event FDA finds a *USP* name to be unduly complex or not useful for some other reason, the agency may conduct notice and comment rulemaking under section 508 of the FD&C Act, and designate a different official name for use in *USP* and *NF*. In contrast to *USP*'s role in designating nonproprietary names, the designation of proprietary (brand) names is solely the responsibility of FDA, working with applicants.

The *USP* Nomenclature Expert Committee, the predecessor to the 2010–2015 Nomenclature, Safety, and Labeling (NSL) Expert Committee, was formed in 1986 to create appropriate established names for dosage forms and combination drug products, and to develop naming policies. Today, the NSL Expert Committee coordinates its work with the USAN Council, and in the great majority of cases retains the existing name given by USAN or FDA. The NSL also establishes the Pronunciation Guide, which is used by USAN.

The USAN Council began in 1961 by providing ingredient names for drugs prior to their marketing. *USP* participates in this activity, together with the American Medical Association, the American Pharmacists Association, and FDA. The Council's output is incorporated into the *USP Dictionary of USAN and International Drug Names* (see *USP Dictionary*, below).

HARMONIZATION ACTIVITIES

Pharmacopeial Discussion Group—*USP* harmonizes pharmacopeial excipient monographs and general chapters

through the Pharmacopeial Discussion Group (PDG), which includes representatives from the European, Japanese, and United States pharmacopeias, and WHO (as an observer). According to the PDG definition, "a pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results, and the same accept/reject decision is reached." General information chapter (1196), *Pharmacopeial Harmonization*, provides (1) the PDG Policy Statement, (2) the PDG Working Procedures and a definition of each stage of harmonization, (3) a discussion, (4) a status report, and (5) a glossary. More information regarding PDG is available on *USP*'s website.

OTHER USP PUBLICATIONS

Chromatographic Columns—This comprehensive reference, previously titled *Chromatographic Reagents*, provides detailed information needed to conduct chromatographic procedures found in *USP–NF*. *Chromatographic Columns* lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic analytical procedures that have been published in *PF* since 1980. *Chromatographic Columns* also helps to track which column reagents were used to validate analytical procedures that have become official. The branded column reagents list is updated bimonthly and maintained on *USP*'s website.

USP Dictionary—The *USP Dictionary of USAN and International Drug Names* provides in a single volume the most up-to-date United States Adopted Names of drugs; official *USP–NF* names; nonproprietary, brand, and chemical names; graphic formulas; molecular formulas and weights; CAS registry numbers and code designations; drug manufacturers; and pharmacologic and therapeutic categories. The *Dictionary* helps to ensure the accuracy of the following: product labeling; reports, articles, and correspondence; FDA regulatory filings; and pharmaceutical package inserts. It is published annually. (See *Nomenclature*.)

USP Dietary Supplements Compendium—The *Dietary Supplements Compendium* combines, in a single volume, *USP–NF* standards for dietary supplements, standards and information from the *Food Chemicals Codex*, regulatory and industry documents, and other tools and resources. It is published every 2 years, as a hardcover print edition.

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USP Medicines Compendium—The *USP Medicines Compendium* (MC) is an online compendium that includes monographs, general chapters, and reference materials for suitable chemical and biological medicines and their ingredients approved by national regulatory authorities. The purpose of the MC is to help ensure that these medicines are of good quality by providing up-to-date, relevant public standards and reference materials. MC standards are available to manufacturers, purchasers, national regulatory authorities, and others to ensure conformity of a medicine to MC standards through testing. The MC does not include standards for foods or for traditional medicines/dietary supplements. The MC is available at www.usp-mc.org.

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USP on Compounding: A Guide for the Compounding Practitioner—*USP on Compounding* is an electronic compen-

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In Memoriam

USP would like to acknowledge the following Expert Volunteers who have passed away during the 2010–2015 Cycle:

Robert G. Bursey, Ph.D. (Monographs—Food Ingredients Expert Committee); Ranga Velagaleti, Ph.D. (Monographs—Food Ingredients Expert Committee)

Admissions

New Articles Appearing in This Supplement

GENERAL CHAPTERS

- | | |
|--|--|
| ⟨208⟩ Anti-Factor Xa and Anti-Factor IIa Assays for Unfractionated and Low Molecular Weight Heparins | ⟨1229.2⟩ Moist Heat Sterilization of Aqueous Liquids |
| ⟨1106⟩ Immunogenicity Assays—Design and Validation of Immunoassays To Detect Anti-Drug Antibodies | ⟨1724⟩ Semi-Solid Drug Products—Performance Tests |
| ⟨1229⟩ Sterilization of Compendial Articles | ⟨2232⟩ Elemental Contaminants in Dietary Supplements |
| ⟨1229.1⟩ Steam Sterilization by Direct Contact | |

Dietary Supplements

- | | |
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| Native Gymnema Extract | Purified Gymnema Extract |

NF 31

- | | |
|------------------------|----------------|
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| Butyl Palmitostearate | Propanediol |

USP 36

- | | |
|--|---|
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| Amoxicillin and Clavulanic Acid Extended-Release Tablets | Irinotecan Hydrochloride Injection |
| Aripiprazole | Latanoprost |
| Atomoxetine Hydrochloride | Lopinavir and Ritonavir Tablets |
| Ciprofloxacin Extended-Release Tablets | Nicardipine Hydrochloride |
| Diphenhydramine Citrate and Ibuprofen Tablets | Quinapril and Hydrochlorothiazide Tablets |
| Dorzolamide Hydrochloride Ophthalmic Solution | Ribavirin Capsules |
| Famciclovir | Vigabatrin |

ANNOTATED LIST

Monographs, General Chapters, Reagents, and Tables Affected by Changes Appearing in This Supplement

Page citations refer to the pages of this Supplement. Note—In the lists below, if a section is new or if a subsection is added to or deleted from an existing section, it is labeled as such in parentheses after the section or subsection name. Items on this list that appear without the designation “new”, “added”, or “deleted” are items in which changes have been made to existing official text.

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GENERAL NOTICES AND REQUIREMENTS

The *General Notices and Requirements* section (the *General Notices*) presents the basic assumptions, definitions, and default conditions for the interpretation and application of the *United States Pharmacopeia* (USP) and the *National Formulary* (NF).

Requirements stated in these *General Notices* apply to all articles recognized in the USP and NF (the “compendia”) and to all general chapters unless specifically stated otherwise. Where the requirements of an individual monograph differ from the *General Notices* or a general chapter, the monograph requirements apply and supersede the requirements of the *General Notices* or the general chapter, whether or not the monograph explicitly states the difference.

1. TITLE AND REVISION

The full title of this publication (consisting of three volumes and including its *Supplements*), is *The Pharmacopeia of the United States of America*, Thirty-Sixth Revision and the *National Formulary*, Thirty-First Edition. These titles may be abbreviated to USP 36, to NF 31, and to USP 36–NF 31. The *United States Pharmacopeia*, Thirty-Sixth Revision, and the *National Formulary*, Thirty-First Edition, supersede all earlier revisions. Where the terms “USP,” “NF,” or “USP–NF” are used without further qualification during the period in which these compendia are official, they refer only to USP 36, NF 31, and any *Supplement(s)* thereto. The same titles, with no further distinction, apply equally to print or electronic presentation of these contents. Although USP and NF are published under one cover and share these *General Notices*, they are separate compendia.

This revision is official beginning May 1, 2013, unless otherwise indicated in specific text.

Supplements to USP and NF are published periodically. *Interim Revision Announcements* are revisions to USP and NF that are published on the USP website. *Interim Revision Announcements* contain official revisions and their effective dates. Announcements of the availability of new USP Reference Standards and announcements of tests or procedures that are held in abeyance pending availability of required USP Reference Standards are also available on the “New Official Text” tab of USP’s website.

Revision Bulletins are revisions to official text or postponements that require expedited publication. They are published on the USP website and generally are official immediately unless otherwise specified in the *Revision Bulletin*.

Errata are corrections to items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirements. *Errata* are effective upon publication.

2. OFFICIAL STATUS AND LEGAL RECOGNITION

2.10. Official Text

Official text is text contained in USP and NF, including monographs, general chapters, and these *General Notices*. Revisions to official text are provided in *Supplements*, *Interim Revision Announcements*, and *Revision Bulletins*. General chapters numbered from 1000 to 1999 are considered interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no mandatory requirements applicable to any official article unless specifically referenced in *General Notices*, a monograph, or a general chapter numbered below 1000. General chapters numbered above 2000 apply only to articles that are

intended for use as dietary ingredients and dietary supplements.

2.20. Official Articles

An *official article* is an article that is recognized in USP or NF. An article is deemed to be recognized and included in a compendium when a monograph for the article is published in the compendium and an official date is generally or specifically assigned to the monograph.

The title specified in a monograph is the *official title* for such article. Other names considered to be synonyms of the official titles may not be used as substitutes for official titles.

Official articles include both *official substances* and *official products*. An *official substance* is a drug substance, excipient, dietary ingredient, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form.

An *official product* is a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided.

2.30. Legal Recognition

The USP and NF are recognized in the laws and regulations of many countries throughout the world. Regulatory authorities may enforce the standards presented in the USP and NF, but because recognition of the USP and NF may vary by country, users should understand applicable laws and regulations. In the United States under the Federal Food, Drug, and Cosmetic Act (FDCA), both USP and NF are recognized as official compendia. A drug with a name recognized in USP–NF must comply with compendial identity standards or be deemed adulterated, misbranded, or both. See, e.g., FDCA § 501(b) and 502(e)(3)(b); also FDA regulations, 21 CFR § 299.5(a&b). To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs. See, e.g., FDCA § 501(b) and 21 CFR § 299.5(c). In addition, to avoid being deemed misbranded, drugs recognized in USP–NF must also be packaged and labeled in compliance with compendial standards. See FDCA § 502(g).

A dietary supplement represented as conforming to specifications in USP will be deemed a misbranded food if it fails to so conform. See FDCA § 403(s)(2)(D).

Enforcement of USP standards is the responsibility of FDA and other government authorities in the U.S. and elsewhere. USP has no role in enforcement.

3. CONFORMANCE TO STANDARDS

3.10. Applicability of Standards

Standards for an article recognized in a USP compendium are expressed in the article’s monograph, applicable general chapters, and *General Notices*. Unless specifically exempted elsewhere in a compendium, the identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, whether incorporated in the monograph itself, in the *General Notices*, or in the applicable general chapters. Early adoption of revised standards is allowed. Where revised standards for an existing article have been published as final approved “official text” (as approved in section 2.10) but are not yet official (six months after publication, unless otherwise specified; see “official date,” section 2.20) compliance with the revised standard shall not preclude a finding or indication of conformance with USP official standards, unless USP specifies

otherwise by prohibiting early adoption in a particular standard.

The standards in the relevant monograph, general chapter(s), and *General Notices* apply at all times in the life of the article from production to expiration. The manufacturer's specifications, and good manufacturing practices generally (including, e.g., Quality by Design initiatives), are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed. Thus, any official article is expected to meet the compendial standards if tested, and any official article actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance.

At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. Frequency of testing and sampling are left to the preferences or direction of those performing compliance testing, and other users of *USP–NF*, including manufacturers, buyers, or regulatory authorities.

Official products are prepared according to recognized principles of good manufacturing practice and from ingredients that meet *USP* or *NF* standards, where standards for such ingredients exist (for dietary supplements, see section 3.10.20).

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.

3.10.10. Applicability of Standards to Drug Products, Drug Substances, and Excipients

The applicable *USP* or *NF* standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. The applicable standard applies to such articles whether or not the added designation "*USP*" or "*NF*" is used. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, or where there is use of synonyms with the intent or effect of suggesting a significant degree of identity with the official title or name.

3.10.20. Applicability of Standards to Medical Devices, Dietary Supplements, and Their Components and Ingredients

An article recognized in *USP* or *NF* shall comply with the compendial standards if the article is a medical device, component intended for a medical device, dietary supplement, dietary ingredient, or other ingredient that is intended for incorporation into a dietary supplement, and is labeled as conforming to the *USP* or *NF*.

Generally, dietary supplements are prepared from ingredients that meet *USP*, *NF*, or *Food Chemicals Codex* standards. Where such standards do not exist, substances may be used in dietary supplements if they have been shown to be of acceptable food grade quality using other suitable procedures.

3.20. Indicating Conformance

A drug product, drug substance, or excipient may use the designation "*USP*" or "*NF*" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article

complies with the identity prescribed in the specified compendium.

When a drug product, drug substance, or excipient differs from the relevant *USP* or *NF* standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.

When a drug product, drug substance, or excipient fails to comply with the identity prescribed in *USP* or *NF* or contains an added substance that interferes with the prescribed tests and procedures, the article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in *USP* or *NF*.

A medical device, dietary supplement, or ingredient or component of a medical device or dietary supplement may use the designation "*USP*" or "*NF*" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the monograph standards and other applicable standards in the compendium.

The designation "*USP*" or "*NF*" on the label may not and does not constitute an endorsement by *USP* and does not represent assurance by *USP* that the article is known to comply with the relevant standards. *USP* may seek legal redress if an article purports to be or is represented as an official article in one of *USP*'s compendia and such claim is determined by *USP* not to be made in good faith.

The designation "*USP–NF*" may be used on the label of an article provided that the label also bears a statement such as "*Meets NF standards as published by USP,*" indicating the particular compendium to which the article purports to apply.

When the letters "*USP*," "*NF*," or "*USP–NF*" are used on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article. The letters are not to be enclosed in any symbol such as a circle, square, etc., and shall appear in capital letters.

If a dietary supplement does not comply with all applicable compendial requirements but contains one or more dietary ingredients or other ingredients that are recognized in *USP* or *NF*, the individual ingredient(s) may be designated as complying with *USP* or *NF* standards or being of *USP* or *NF* quality provided that the designation is limited to the individual ingredient(s) and does not suggest that the dietary supplement complies with *USP* standards.

4. MONOGRAPHS AND GENERAL CHAPTERS

4.10. Monographs

Monographs set forth the article's name, definition, specification, and other requirements related to packaging, storage, and labeling. The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and purity of the article. For general requirements relating to specific monograph sections, see section 5, *Monograph Components*.

Because monographs may not provide standards for all relevant characteristics, some official substances may conform to the *USP* or *NF* standard but differ with regard to nonstandardized properties that are relevant to their use in specific preparations. To assure interchangeability in such instances, users may wish to ascertain functional equivalence or determine such characteristics before use.

4.10.10. Applicability of Test Procedures

A single monograph may include several different tests, procedures, and/or acceptance criteria that reflect attributes of different manufacturers' articles. Such alternatives may be presented for different polymorphic forms, impurities, hydrates, and dissolution cases. Monographs indicate the tests, procedures, and/or acceptance criteria to be used and the required labeling.

A test in a monograph may contain and require multiple procedures. However, multiple procedures may be included in particular monographs specifically for the purpose of assuring the availability of an appropriate procedure for a par-

ticular product. In such cases, a labeling statement to indicate the appropriate application of the procedure(s) will be included in the monograph. A labeling statement is not required if Test 1 is used.

4.10.20. Acceptance Criteria

The acceptance criteria allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. The existence of compendial acceptance criteria does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity “exceeds” compendial quality. Similarly, the fact that an article has been prepared to tighter criteria than those specified in the monograph does not constitute a basis for a claim that the article “exceeds” the compendial requirements.

An official product shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. Where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, the upper acceptance criterion contained in the monograph may be increased by a corresponding amount.

The acceptance criteria specified in individual monographs and in the general chapters for compounded preparations are based on such attributes of quality as might be expected to characterize an article compounded from suitable bulk drug substances and ingredients, using the procedures provided or recognized principles of good compounding practice, as described in these compendia.

4.20. General Chapters

Each general chapter is assigned a number that appears in angle brackets adjacent to the chapter name (e.g., *Chromatography* (621)). General chapters may contain the following:

- Descriptions of tests and procedures for application through individual monographs,
- Descriptions and specifications of conditions and practices for pharmaceutical compounding,
- General information for the interpretation of the compendial requirements,
- Descriptions of general pharmaceutical storage, dispensing, and packaging practices, or
- General guidance to manufacturers of official substances or official products.

When a general chapter is referenced in a monograph, acceptance criteria may be presented after a colon.

Some chapters may serve as introductory overviews of a test or of analytical techniques. They may reference other general chapters that contain techniques, details of the procedures, and, at times, acceptance criteria.

5. MONOGRAPH COMPONENTS

5.10. Molecular Formula

The use of the molecular formula for the active ingredient(s) named in defining the required strength of a compendial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

5.20. Added Substances

Added substances are presumed to be unsuitable for inclusion in an official article and therefore prohibited, if: (1) they exceed the minimum quantity required for providing their intended effect; (2) their presence impairs the bioavailability, therapeutic efficacy, or safety of the official article; or (3) they interfere with the assays and tests prescribed for determining compliance with the compendial standards.

The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.

5.20.10. Added Substances, Excipients, and Ingredients in Official Substances

Official substances may contain only the specific added substances that are permitted by the individual monograph. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s).

5.20.20. Added Substances, Excipients, and Ingredients in Official Products

Suitable substances and excipients such as antimicrobial agents, pharmaceutical bases, carriers, coatings, flavors, preservatives, stabilizers, and vehicles may be added to an official product to enhance its stability, usefulness, or elegance, or to facilitate its preparation, unless otherwise specified in the individual monograph.

Added substances and excipients employed solely to impart color may be incorporated into official products other than those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the U.S. Food and Drug Administration (FDA), provided such added substances or excipients are otherwise appropriate in all respects. (See also *Added Substances under Injections* (1).)

The proportions of the substances constituting the base in ointment and suppository products and preparations may be varied to maintain a suitable consistency under different climatic conditions, provided that the concentrations of active ingredients are not varied and provided that the bioavailability, therapeutic efficacy, and safety of the preparation are not impaired.

5.20.20.1. In Compounded Preparations

Compounded preparations for which a complete composition is given shall contain only the ingredients named in the formulas unless specifically exempted herein or in the individual monograph. Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process.

Where a monograph for a compounded preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried before use if due allowance is made for the water or other volatile substances present in the quantity taken.

Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of official preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A preparation that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a usual ingredient in the preparation or a permissible added substance; in either case the denaturant shall be identified on the label of the topical preparation. Where a process is given in the individual monograph, any preparation compounded using denatured alcohol shall be identical to that prepared by the monograph process.

5.20.20.2. In Dietary Supplements

Additional ingredients may be added to dietary supplement products provided that the additional ingredients: (1) comply with applicable regulatory requirements; and (2) do not interfere with the assays and tests prescribed for determining compliance with compendial standards.

5.30. Description and Solubility

Only where a quantitative solubility test is given in a monograph and is designated as such is it a test for purity.

A monograph may include information regarding the article's description. Information about an article's “description and solubility” also is provided in the reference table *Description and Relative Solubility of USP and NF Articles*. The reference table merely denotes the properties of articles that comply with monograph standards. The reference table is

intended primarily for those who use, prepare, and dispense drugs and/or related articles. Although the information provided in monographs and the information in the reference table may indirectly assist in the preliminary evaluation of an article, it is not intended to serve as a standard or test for purity.

The approximate solubility of a compendial substance is indicated by one of the following descriptive terms:

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

5.40. Identity

A compendial test titled *Identity* or *Identification* is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers, and to establish whether it is the article named in *USP–NF*. The *Identity* or *Identification* test for a particular article may consist of one or more procedures. When a compendial test for *Identity* or *Identification* is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test. Failure of an article to meet all the requirements of a prescribed *Identity* or *Identification* test (i.e., failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.

5.50. Assay

Assay tests for compounded preparations are not intended for evaluating a compounded preparation before dispensing, but instead are intended to serve as the official test in the event of a question or dispute regarding the preparation's conformance to official standards.

5.50.10. Units of Potency (Biological)

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as "USP Units." For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined (see *Biologics* <1041>).

5.60. Impurities and Foreign Substances

Tests for the presence of impurities and foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* <1086>).

Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practice.

5.60.10. Other Impurities in USP and NF Articles

If a *USP* or *NF* monograph includes an assay or organic impurity test based on chromatography, other than a test for residual solvents, and that monograph procedure does not detect an impurity present in the substance, the amount and identity of the impurity, where both are known, shall be stated in the labeling (certificate of analysis) of the official substance, under the heading *Other Impurity(ies)*.

The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all *Other Impurities* combined with the monograph-detected impurities may not exceed 2.0% (see *Ordinary Impurities* <466>), unless otherwise stated in the monograph.

The following categories of drug substances are excluded from *Other Impurities* requirements:

- fermentation products and semi-synthetics derived therefrom,
- radiopharmaceuticals,
- biologics,
- biotechnology-derived products,
- peptides,
- herbals, and
- crude products of animal or plant origin.

Any substance known to be toxic shall not be listed under *Other Impurities*.

5.60.20. Residual Solvents in USP and NF Articles

All *USP* and *NF* articles are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. If solvents are used during production, they must be of suitable quality. In addition, the toxicity and residual level of each solvent shall be taken into consideration, and the solvents limited according to the principles defined and the requirements specified in *Residual Solvents* <467>, using the general methods presented therein or other suitable methods.

5.70. Performance Tests

Where content uniformity determinations have been made using the same analytical methodology specified in the Assay, with appropriate allowances made for differences in sample preparation, the average of all of the individual content uniformity determinations may be used as the Assay value.

5.80. USP Reference Standards

USP Reference Standards are authentic specimens that have been approved as suitable for use as comparison standards in *USP* or *NF* tests and assays. (See *USP Reference Standards* <11>.) Where a procedure calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article shall be used. If any new *USP* or *NF* standard requires the use of a new USP Reference Standard that is not yet available, that portion of the standard containing the requirement shall not be official until the specified USP reference material is available.

Unless a reference standard label bears a specific potency or content, assume the reference standard is 100.0% pure in the official application. Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP Reference Standards are to be used in accordance with the instructions on the label of the Reference Standard.

6. TESTING PRACTICES AND PROCEDURES

6.10. Safe Laboratory Practices

In performing compendial procedures, safe laboratory practices shall be followed, including precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures used. Before undertaking any procedure described in the compendia, the analyst should be aware of the hazards associated with the chemicals and the techniques and means of protecting against them. These compendia are not designed to describe such hazards or protective measures.

6.20. Automated Procedures

Automated and manual procedures employing the same basic chemistry are considered equivalent.

6.30. Alternative and Harmonized Methods and Procedures

Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in the general chapter *Validation of Compendial Procedures* (1225) and must be shown to give equivalent or better results. Only those results obtained by the methods and procedures given in the compendium are conclusive.

Alternative procedures should be submitted to USP for evaluation as a potential replacement or addition to the standard (see section 4.10, *Monographs*).

Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method or procedure from one of these pharmacopoeias, it should comply with the requirements of the *USP*. When a difference appears, or in the event of dispute, only the result obtained by the method and/or procedure given in the *USP* is conclusive.

6.40. Dried, Anhydrous, Ignited, or Solvent-Free Basis

All calculations in the compendia assume an “as-is” basis unless otherwise specified.

Test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on Drying*, or *Water*, or *Loss on Ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

The term “solvent-free” signifies that the calculation shall be corrected for the presence of known solvents as determined using the methods described in *Residual Solvents* (467) unless a test for limit of organic solvents is provided in the monograph.

The term “previously dried” without qualification signifies that the substance shall be dried as directed under *Loss on Drying* (731) or *Water Determination* (921) (gravimetric determination).

Where drying in vacuum over a desiccant is directed, a vacuum desiccator, a vacuum drying pistol, or other suitable vacuum drying apparatus shall be used.

6.40.10. Ignite To Constant Weight

“Ignite to constant weight” means that ignition shall be continued at $800 \pm 25^\circ$, unless otherwise indicated, until two consecutive weighings, the second of which is taken after an additional period appropriate to the nature and quantity of the residue, do not differ by more than 0.50 mg per g of substance taken.

6.40.20. Dried To Constant Weight

“Dried to constant weight” means that drying shall be continued until two consecutive weighings, the second of which is taken after an additional drying period appropriate to the nature and quantity of the residue, do not differ by more than 0.50 mg per g of substance taken.

6.50. Preparation of Solutions**6.50.10. Filtration**

Where a procedure gives direction to “filter” without further qualification, the liquid shall be passed through suitable filter paper or equivalent device until the filtrate is clear. Due to the possibility of filter effects, the initial volumes of a filtrate may be discarded.

6.50.20. Solutions

Unless otherwise specified, all solutions shall be prepared with Purified Water. Solutions for quantitative measures shall

be prepared using accurately weighed or accurately measured analytes (see section 8.20, *About*).

An expression such as “(1 in 10)” means that 1 part *by volume* of a liquid shall be diluted with, or 1 part *by weight* of a solid shall be dissolved in, a sufficient quantity of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*. An expression such as “(20:5:2)” means that the respective numbers of parts, by volume, of the designated liquids shall be mixed, unless otherwise indicated.

6.50.20.1. Adjustments to Solutions

When a specified concentration is called for in a procedure, a solution of other normality or molarity may be used, provided that allowance is made for the difference in concentration and that the change does not increase the error of measurement.

Unless otherwise indicated, analyte concentrations shall be prepared to within ten percent (10%) of the indicated value. In the special case in which a procedure is adapted to the working range of an instrument, solution concentrations may differ from the indicated value by more than ten percent (10%), with appropriate changes in associated calculations. Any changes shall fall within the validated range of the instrument.

When adjustment of pH is indicated with either an acid or base and the concentration is not indicated, appropriate concentrations of that acid or base may be used.

6.50.20.2. Test Solutions

Information on Test Solutions (TS) is provided in the *Test Solutions* portion of the *Reagents, Indicators, and Solutions* section of the *USP–NF*. Use of an alternative Test Solution or a change in the Test Solution used may require validation.

6.50.20.3. Indicator Solutions

Where a procedure specifies the use of an indicator TS, approximately 0.2 mL, or 3 drops, of the solution shall be added unless otherwise directed.

6.60. Units Necessary to Complete a Test

Unless otherwise specified, a sufficient number of units to ensure a suitable analytical result shall be taken.

6.60.10. Tablets

Where the procedure of a Tablet monograph directs to weigh and finely powder not fewer than a given number of Tablets, a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered Tablets taken shall be representative of the whole Tablets and shall, in turn, be weighed accurately.

6.60.20. Capsules

Where the procedure of a Capsule monograph gives direction to remove, as completely as possible, the contents of not fewer than a given number of the Capsules, a counted number of Capsules shall be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken shall be representative of the contents of the Capsules and shall, in turn, be weighed accurately.

6.70. Reagents

The proper conduct of the compendial procedures and the reliability of the results depend, in part, upon the quality of the reagents used in the performance of the procedures. Unless otherwise specified, reagents conforming to the specifications set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society (ACS) shall be used. Where such ACS reagent specifications are not available or where the required purity differs, compendial specifications for reagents of acceptable quality are provided (see the *Reagents, Indicators, and Solutions* section of the *USP–NF*). Reagents not covered by any of these specifications should be of a grade suitable to the proper performance of the method of assay or test involved.

Listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutic utility; furthermore, any reference to *USP* or *NF* in their labeling shall include also the term “reagent”

or “reagent grade.” USP may supply reagents if they otherwise may not be generally commercially available.

6.80. Equipment

Unless otherwise specified, a specification for a definite size or type of container or apparatus in a procedure is given solely as a recommendation. Other dimensions or types may be used if they are suitable for the intended use.

6.80.10. Apparatus for Measurement

Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed.

6.80.10.1. Pipet

Where a pipet is specified, a suitable buret may be substituted. Where a “to contain” pipet is specified, a suitable volumetric flask may be substituted.

6.80.10.2. Light Protection

Where low-actinic or light-resistant containers are specified, either containers specially treated to protect contents from light or clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

6.80.20. Instrumental Apparatus

An instrument may be substituted for the specified instrument if the substitute uses the same fundamental principles of operation and is of equivalent or greater sensitivity and accuracy. These characteristics shall be qualified as appropriate. Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification.

6.80.20.1. Chromatographic Tubes and Columns

The term “diameter” refers to internal diameter (ID).

6.80.20.2. Tubing

The term “diameter” refers to outside diameter (OD).

6.80.20.3. Steam Bath

Where use of a steam bath is directed, use actively flowing steam or another regulated heat source controlled at an equivalent temperature.

6.80.20.4. Water Bath

A water bath requires vigorously boiling water unless otherwise specified.

7. TEST RESULTS

7.10. Interpretation of Requirements

Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated acceptance criteria to determine whether the article conforms to compendial requirements.

The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented.

Where acceptance criteria are expressed numerically herein through specification of an upper and/or lower limit, permitted values include the specified values themselves, but no values outside the limit(s). Acceptance criteria are considered significant to the last digit shown.

7.10.5. Nominal Concentrations in Equations

Where a “nominal concentration” is specified, calculate the concentration based on the label claim. In assay procedures, water correction is typically stated in the Definition and on the label of the USP Reference Standard. For other procedures, correction for assayed content, potency, or both is made prior to using the concentration in the equation provided in the monograph.

7.10.10. Equivalence Statements in Titrimetric Procedures

The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, the number of significant figures in the concentration of the titrant should be understood to correspond to the number of significant figures in the weight of the analyte. Corrections to calculations based on the blank determination are to be made for all titrimetric assays where appropriate (see *Titrimetry* (541)).

7.20. Rounding Rules

The observed or calculated values shall be rounded off to the number of decimal places that is in agreement with the limit expression. Numbers should not be rounded until the final calculations for the reportable value have been completed. Intermediate calculations (e.g., slope for linearity) may be rounded for reporting purposes, but the original (not rounded) value should be used for any additional required calculations. Acceptance criteria are fixed numbers and are not rounded.

When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1.

8. TERMS AND DEFINITIONS

8.10. Abbreviations

- RS refers to a USP Reference Standard.
- CS refers to a Colorimetric Solution.
- TS refers to a Test Solution.
- VS refers to a Volumetric Solution that is standardized in accordance with directions given in the individual monograph or in the *Reagents, Indicators, and Solutions* section of USP–NF.

8.20. About

“About” indicates a quantity within 10%.

If the measurement is stated to be “accurately measured” or “accurately weighed,” follow the statements in the gen-

**Illustration of Rounding Numerical Values
for Comparison with Requirements**

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit $\geq 98.0\%$	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit $\leq 101.5\%$	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test $\leq 0.02\%$	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤ 3 ppm	3.5 ppm	4 ppm	No
	3.4 ppm	3 ppm	Yes
	2.5 ppm	3 ppm	Yes

eral chapters *Volumetric Apparatus* (31) and *Weights and Balances* (41), respectively.

8.30. Alcohol Content

Percentages of alcohol, such as those under the heading *Alcohol Content*, refer to percentage by volume of C_2H_5OH at 15.56°. Where a formula, test, or assay calls for alcohol, ethyl alcohol, or ethanol, the *USP* monograph article Alcohol shall be used. Where reference is made to " C_2H_5OH ," absolute (100 percent) ethanol is intended. Where a procedure calls for dehydrated alcohol, alcohol absolute, or anhydrous alcohol, the *USP* monograph article Dehydrated Alcohol shall be used.

8.40. Atomic Weights

Atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those established by the IUPAC Commission on Atomic Weights and Isotopic Abundances.

8.50. Blank Determinations

Where it is directed that "any necessary correction" be made by a blank determination, the determination shall be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

8.60. Concomitantly

"Concomitantly" denotes that the determinations or measurements are to be performed in immediate succession.

8.70. Desiccator

The instruction "in a desiccator" indicates use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of a suitable desiccant such as anhydrous calcium chloride, magnesium perchlorate, phosphorus pentoxide, or silica gel. See also section 8.220, *Vacuum Desiccator*.

8.80. Logarithms

Logarithms are to the base 10.

8.90. Microbial Strain

A microbial strain cited and identified by its ATCC catalog number shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

8.100. Negligible

"Negligible" indicates a quantity not exceeding 0.50 mg.

8.110. NLT/NMT

"NLT" means "not less than." "NMT" means "not more than."

8.120. Odor

"Odorless," "practically odorless," "a faint characteristic odor," and variations thereof indicate evaluation of a suitable quantity of freshly opened material after exposure to the air for 15 minutes. An odor designation is descriptive only and should not be regarded as a standard of purity for a particular lot of an article.

8.130. Percent

"Percent" used without qualification means:

- For mixtures of solids and semisolids, percent weight in weight;
- For solutions or suspensions of solids in liquids, percent weight in volume;
- For solutions of liquids in liquids, percent volume in volume;
- For solutions of gases in liquids, percent weight in volume.

For example, a 1 percent solution is prepared by dissolving 1 g of a solid or semisolid, or 1 mL of a liquid, in sufficient solvent to make 100 mL of the solution.

8.140. Percentage Concentrations

Percentage concentrations are expressed as follows:

- *Percent Weight in Weight* (w/w) is defined as the number of g of a solute in 100 g of solution.

- *Percent Weight in Volume* (w/v) is defined as number of g of a solute in 100 mL of solution.
- *Percent Volume in Volume* (v/v) is defined as the number of mL of a solute in 100 mL of solution.

8.150. Pressure

Pressure is determined by use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

8.160. Reaction Time

Reaction time is 5 minutes unless otherwise specified.

8.170. Specific Gravity

Specific gravity is the weight of a substance in air at 25° divided by the weight of an equal volume of water at the same temperature.

8.180. Temperatures

Temperatures are expressed in centigrade (Celsius) degrees, and all measurements are made at 25° unless otherwise indicated. Where moderate heat is specified, any temperature not higher than 45° (113° F) is indicated.

8.190. Time

Unless otherwise specified, rounding rules, as described in section 7.20, *Rounding Rules*, apply to any time specified.

8.200. Transfer

"Transfer" indicates a quantitative manipulation.

8.210. Vacuum

"Vacuum" denotes exposure to a pressure of less than 20 mm of mercury (2.67 kPa), unless otherwise indicated.

8.220. Vacuum Desiccator

"Vacuum desiccator" indicates a desiccator that maintains a low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury (2.67 kPa) or at the pressure designated in the individual monograph.

8.230. Water

8.230.10. Water as an Ingredient in an Official Product

As an ingredient in an official product, water meets the requirements of the appropriate water monograph in *USP* or *NF*.

8.230.20. Water in the Manufacture of Official Substances

When used in the manufacture of official substances, water may meet the requirements for drinking water as set forth in the regulations of the U.S. Environmental Protection Agency (potable water).

8.230.30. Water in a Compendial Procedure

When water is called for in a compendial procedure, the *USP* article Purified Water shall be used unless otherwise specified. Definitions for *High-Purity Water* and *Carbon Dioxide-Free Water* are provided in *Containers—Glass* (660). Definitions of other types of water are provided in *Water for Pharmaceutical Purposes* (1231).

8.240. Weights and Measures

In general, weights and measures are expressed in the International System of Units (SI) as established and revised by the *Conférence générale des poids et mesures*. For compendial purposes, the term "weight" is considered to be synonymous with "mass."

Molality is designated by the symbol *m* preceded by a number that represents the number of moles of the designated solute contained in 1 kilogram of the designated solvent.

Molarity is designated by the symbol *M* preceded by a number that represents the number of moles of the designated solute contained in an amount of the designated solvent that is sufficient to prepare 1 liter of solution.

Normality is designated by the symbol *N* preceded by a number that represents the number of equivalents of the designated solute contained in an amount of the designated solvent that is sufficient to prepare 1 liter of solution.

Symbols commonly employed for SI metric units and other units are as follows:

Bq = becquerel	dL = deciliter
kBq = kilobecquerel	L = liter
MBq = megabecquerel	mL = milliliter ^c
GBq = gigabecquerel	μL = microliter
Ci = curie	Eq = gram-equivalent weight
mCi = millicurie	mEq = milliequivalent
μCi = microcurie	mol = gram-molecular weight (mole)
nCi = nanocurie	Da = dalton (relative molecular mass)
Gy = gray	mmol = millimole
mGy = milligray	Osmol = osmole
m = meter	mOsmol = milliosmole
dm = decimeter	Hz = hertz
cm = centimeter	kHz = kilohertz
mm = millimeter	MHz = megahertz
μm = micrometer (0.001 mm)	V = volts
nm = nanometer ^a	MeV = million electron volts
kg = kilogram	keV = kilo-electron volt
g = gram	mV = millivolt
mg = milligram	psi = pounds per square inch
μg; mcg = microgram ^b	Pa = pascal
ng = nanogram	kPa = kilopascal
pg = picogram	g = gravity (in centrifugation)
fg = femtogram	

^a Previously the symbol mμ (for millimicron) was used.

^b The symbol μg is used in the *USP* and *NF* to represent micrograms, but micrograms may be represented as "mcg" for labeling and prescribing purposes. The term "gamma," symbolized by γ, frequently is used to represent micrograms in biochemical literature.

^c One milliliter (mL) is used herein as the equivalent of one cubic centimeter (cc).

9. PRESCRIBING AND DISPENSING

9.10 Use of Metric Units

Prescriptions for compendial articles shall be written to state the quantity and/or strength desired in metric units unless otherwise indicated in the individual monograph (see also *Units of Potency*, section 5.50.10 above). If an amount is prescribed by any other system of measurement, only an amount that is the metric equivalent of the prescribed amount shall be dispensed. Apothecary unit designations on labels and labeling shall not be used.

9.20 Changes in Volume

In the dispensing of prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.

10. PRESERVATION, PACKAGING, STORAGE, AND LABELING

10.10. Storage Under Nonspecific Conditions

If no specific directions or limitations are provided in the *Packaging and Storage* section of an individual *USP* monograph or in the labeling of an article recognized in *USP*, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Such articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Drug substances are exempt from the requirements in this paragraph.

Regardless of quantity, where no specific storage directions or limitations are provided in an individual *NF* monograph or stated in the labeling of an article recognized in *NF*, the conditions of storage and distribution shall include protection from moisture, freezing, excessive heat, and, where necessary, from light.

10.20. Containers

The container is that which holds the article and is or may be in direct contact with the article. The immediate container is that which is in direct contact with the article at all times. The closure is a part of the container.

Before being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The compendial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

10.20.10. Tamper-Evident Packaging

The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-evident packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging used by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

10.20.20. Light-Resistant Container

A light-resistant container (see *Light Transmission Test* under *Containers—Performance Testing* (671)) protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering before dispensing.

10.20.30. Well-Closed Container

A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

10.20.40. Tight Container

A tight container protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution; and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-Index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

[NOTE—Where packaging and storage in a *tight container* or a *well-closed container* is specified in the individual monograph, the container used for an article when dispensed on prescription meets the requirements under *Containers—Performance Testing* (671).]

10.20.50. Hermetic Container

A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

10.20.60. Single-Unit Container

A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

10.20.70. Single-Dose Container

A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled. (See also *Containers for Injections* under *Injections* (1).)

10.20.80. Unit-Dose Container

A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

10.20.90. Unit-of-Use Container

A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

10.20.100. Multiple-Unit Container

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

10.20.110. Multiple-Dose Container

A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only. (See also *Containers for Injections* under *Injections* (1).)

10.20.120. Requirements under the Poison Prevention Packaging Act (PPPA)

This act (see the website, www.cpsc.gov/businfo/pppa.html) requires special packaging of most human oral prescription drugs, oral controlled drugs, certain non-oral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations in order to protect the public from personal injury or illness from misuse of these preparations (16 CFR § 1700.14).

The immediate packaging of substances regulated under the PPPA shall comply with the special packaging standards (16 CFR § 1700.15 and 16 CFR § 1700.20). The PPPA regulations for special packaging apply to all packaging types including reclosable, nonclosable, and unit-dose types.

Special packaging is not required for drugs dispensed within a hospital setting for inpatient administration. Manufacturers and packagers of bulk-packaged prescription drugs do not have to use special packaging if the drug will be repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in non-child-resistant packaging upon the request of the purchaser or when directed in a legitimate prescription (15 U.S.C. § 1473).

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in non-child-resistant packaging as long as popular-size, special packages are also supplied. The non-child-resistant package requires special labeling (16 CFR § 1700.5).

Various types of child-resistant packages are covered in ASTM International Standard D-3475, *Standard Classification of Child-Resistant Packaging*. Examples are included as an aid in the understanding and comprehension of each type of classification.

10.30. Storage Temperature and Humidity

Specific directions are stated in some monographs with respect to the temperatures and humidity at which official articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply. The conditions are defined by the following terms.

10.30.10. Freezer

"Freezer" indicates a place in which the temperature is maintained thermostatically between -25° and -10° (-13° and 14° F).

10.30.20. Cold

Any temperature not exceeding 8° (46° F) is "cold." A "refrigerator" is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46° F).

10.30.30. Cool

Any temperature between 8° and 15° (46° and 59° F) is "cool." An article for which storage in a *cool place* is directed may, alternatively, be stored and distributed in a *refrigerator*, unless otherwise specified by the individual monograph.

10.30.40. Controlled Cold Temperature

"Controlled cold temperature" is defined as temperature maintained thermostatically between 2° and 8° (36° and 46° F), that allows for excursions in temperature between 0° and 15° (32° and 59° F) that may be experienced during storage, shipping, and distribution such that the allowable calculated mean kinetic temperature is not more than 8° (46° F). Transient spikes up to 25° (77° F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise.

10.30.50. Room Temperature

"Room temperature" indicates the temperature prevailing in a working area.

10.30.60. Controlled Room Temperature

"Controlled room temperature" indicates a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77° F); that results in a mean kinetic temperature calculated to be not more than 25° ; and that allows for excursions between 15° and 30° (59° and 86° F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40° are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25° ", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations.

An article for which storage at *controlled room temperature* is directed may, alternatively, be stored and distributed in a *cool place*, unless otherwise specified in the individual monograph or on the label.

10.30.70. Warm

Any temperature between 30° and 40° (86° and 104° F) is "warm."

10.30.80. Excessive Heat

"Excessive heat" means any temperature above 40° (104° F).

10.30.90. Protection From Freezing

Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

10.30.100. Dry Place

The term “dry place” denotes a place that does not exceed 40% average relative humidity at *Controlled Room Temperature* or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value is 40% relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered storage in a dry place.

10.40. Labeling

The term “labeling” designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term “label” designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in these compendia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the compendial requirements set forth for the articles.

10.40.10. Amount of Ingredient Per Dosage Unit

The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Official articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* (698). Official drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see 8.140., *Percentage Concentrations*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units. See also 5.50.10., *Units of Potency (Biological)*.

10.40.20. Use of Leading and Terminal Zeros

To help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than 1

shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

10.40.30. Labeling of Salts of Drugs

It is an established principle that official articles shall have only one official title. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids, but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

10.40.40. Labeling Vitamin-Containing Products

The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

10.40.50. Labeling Botanical-Containing Products

The label of an herb or other botanical intended for use as a dietary supplement bears the statement, “If you are pregnant or nursing a baby, seek the advice of a health professional before using this product.”

10.40.60. Labeling Parenteral And Topical Preparations

The label of a preparation intended for parenteral or topical use states the names of all added substances (see 5.20., *Added Substances, Excipients, and Ingredients* and see *Labeling under Injections* (1)), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

10.40.70. Labeling Electrolytes

The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

10.40.80. Labeling Alcohol

The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C₂H₅OH.

10.40.90. Special Capsules and Tablets

The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it shall be used.

10.40.100. Expiration Date and Beyond-Use Date

The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., “EXP 6/08,” “Exp. June 08,” or “Expires 6/08”). [NOTE—For additional information and guidance, refer to the Consumer Healthcare Products Association’s *Voluntary Codes and Guidelines of the Self-Medication Industry*.]

The monographs for some preparations state how the expiration date that shall appear on the label shall be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale

without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the compendial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article shall not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the *General Notices*. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution before use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser shall maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°. The

plastic material used in packaging the dosage forms shall afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records shall be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

10.40.100.1. Compounded Preparations

The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

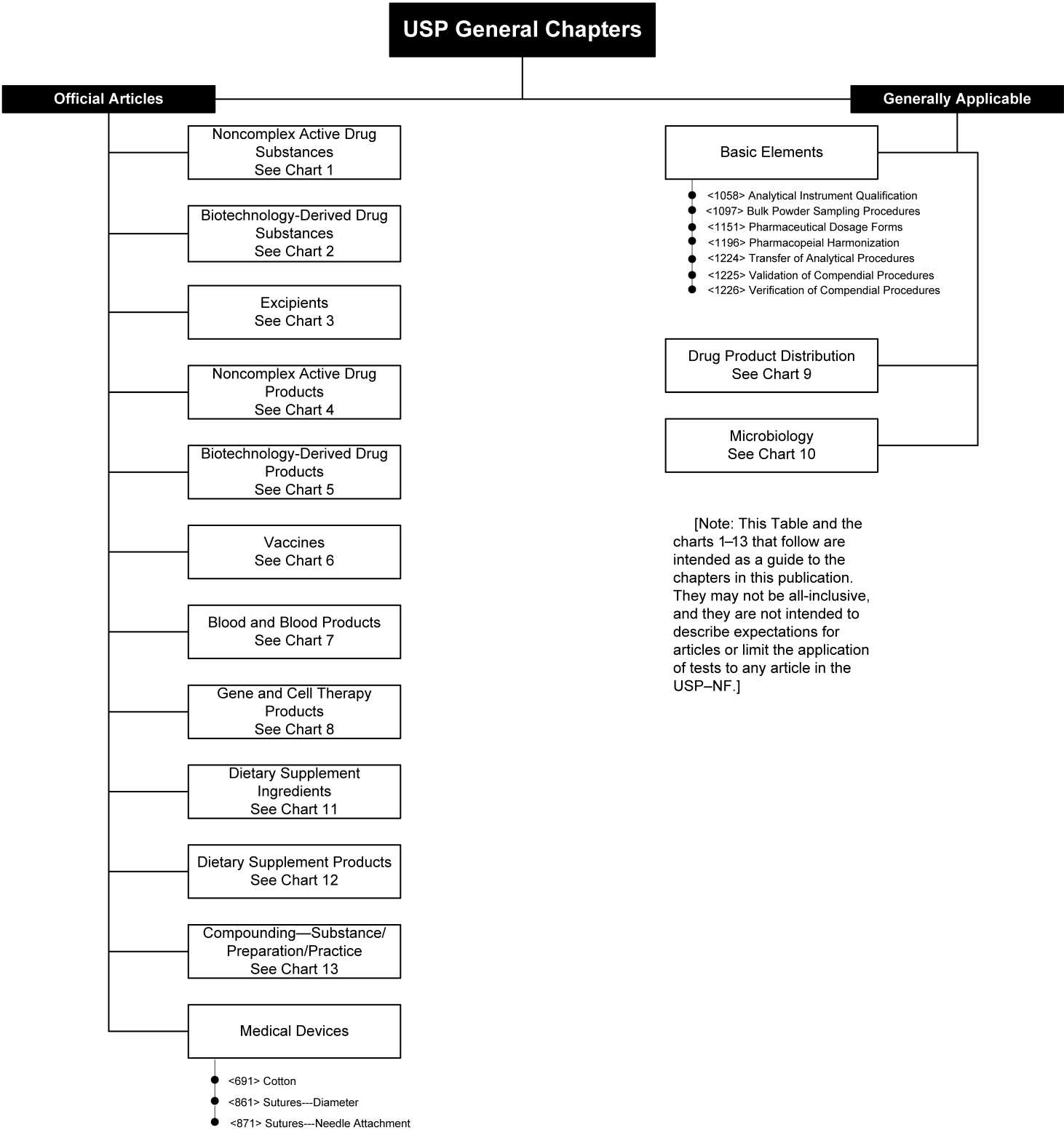
The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, may be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see *Stability Criteria and Beyond-Use Dating under Stability of Compounded Preparations* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* (795)).

10.50. Guidelines for Packaging and Storage Statements in USP–NF Monographs

In order to provide users of the *USP* and *NF* with proper guidance on how to package and store official articles, every monograph in the *USP* and *NF* shall have a packaging and storage specification.

For the packaging portion of the statement, the choice of containers is given in this section 10, *Preservation, Packaging, Storage, and Labeling*, and includes *Light-Resistant Container*, *Well-Closed Container*, *Tight Container*, *Hermetic Container*, *Single-Unit Container*, *Single-Dose Container*, *Unit-Dose Container*, and *Unit-of-Use Container*. For most preparations, the choice is determined by the container in which it shall be dispensed (e.g., tight, well-closed, hermetic, unit-of-use, etc.). For drug substances, the choice would appear to be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical nature as large-volume commodity items, with containers ranging from drums to tank cars, a well-closed container is an appropriate default. Therefore, in the absence of data indicating a need for a more protective class of container, the phrase "Preserve in well-closed containers" should be used as a default for excipients.

Chart Guide



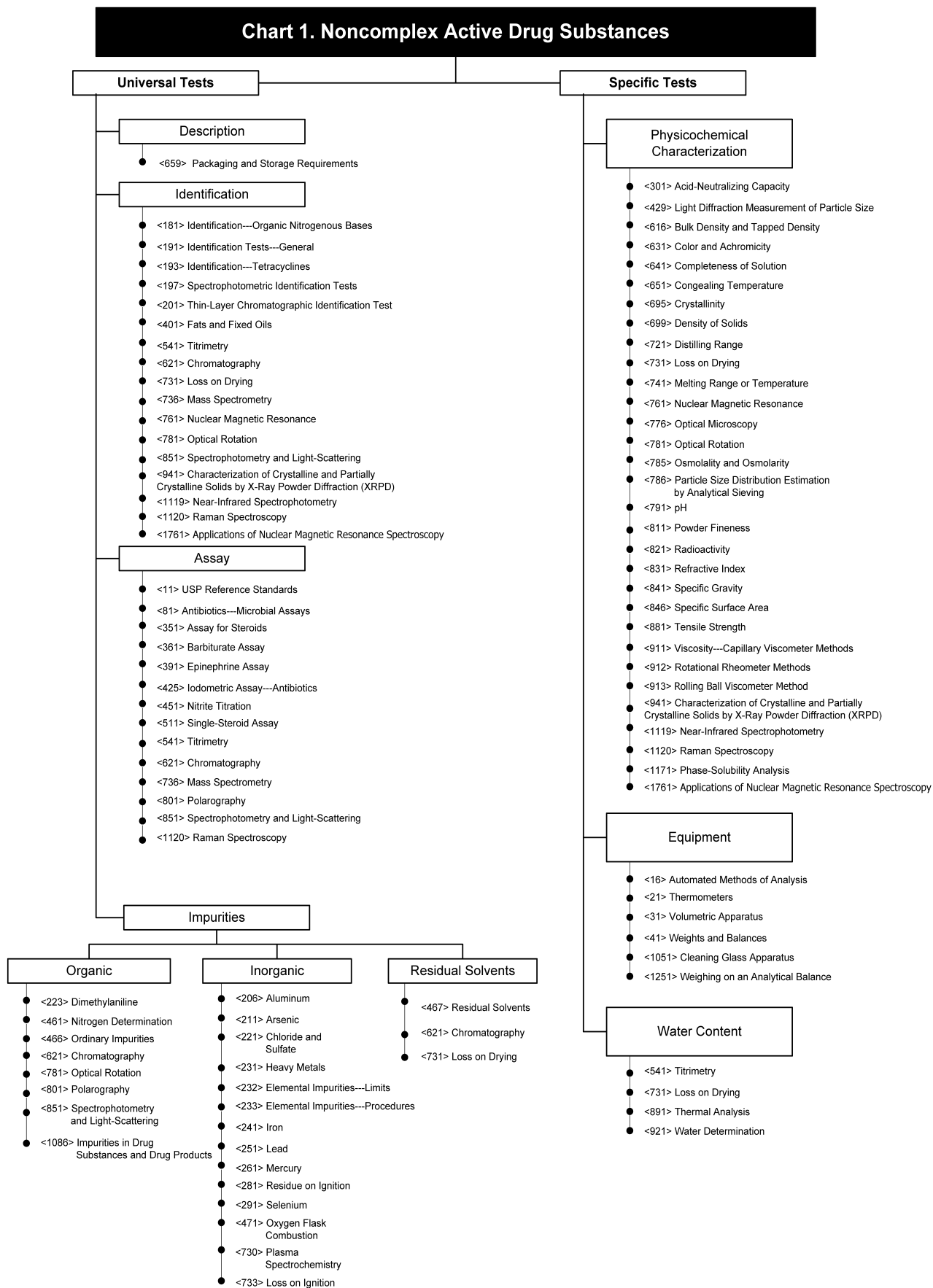


Chart 2. Biotechnology-Derived Drug Substances

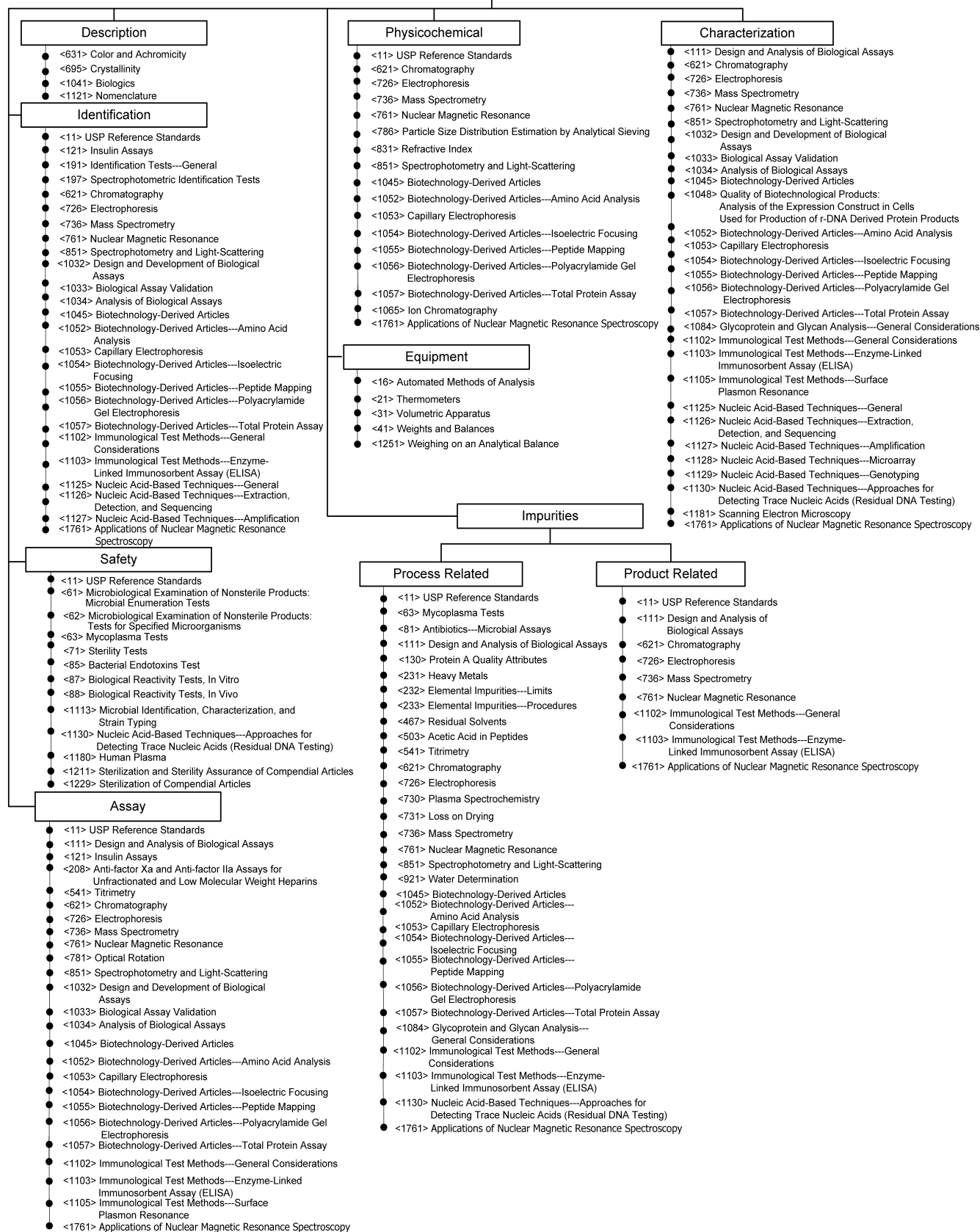


Chart 3. Excipients

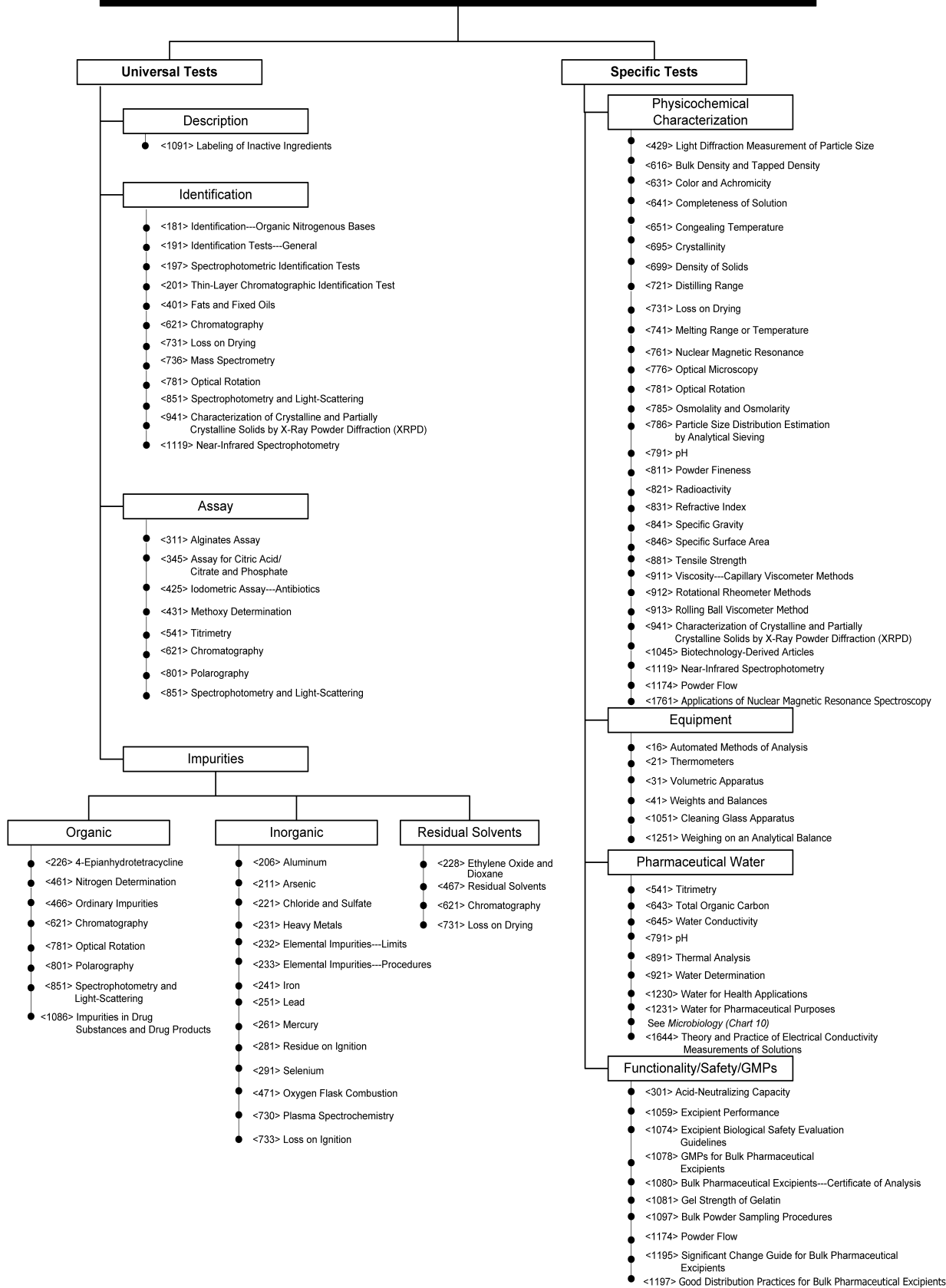


Chart 4. Noncomplex Active Drug Products

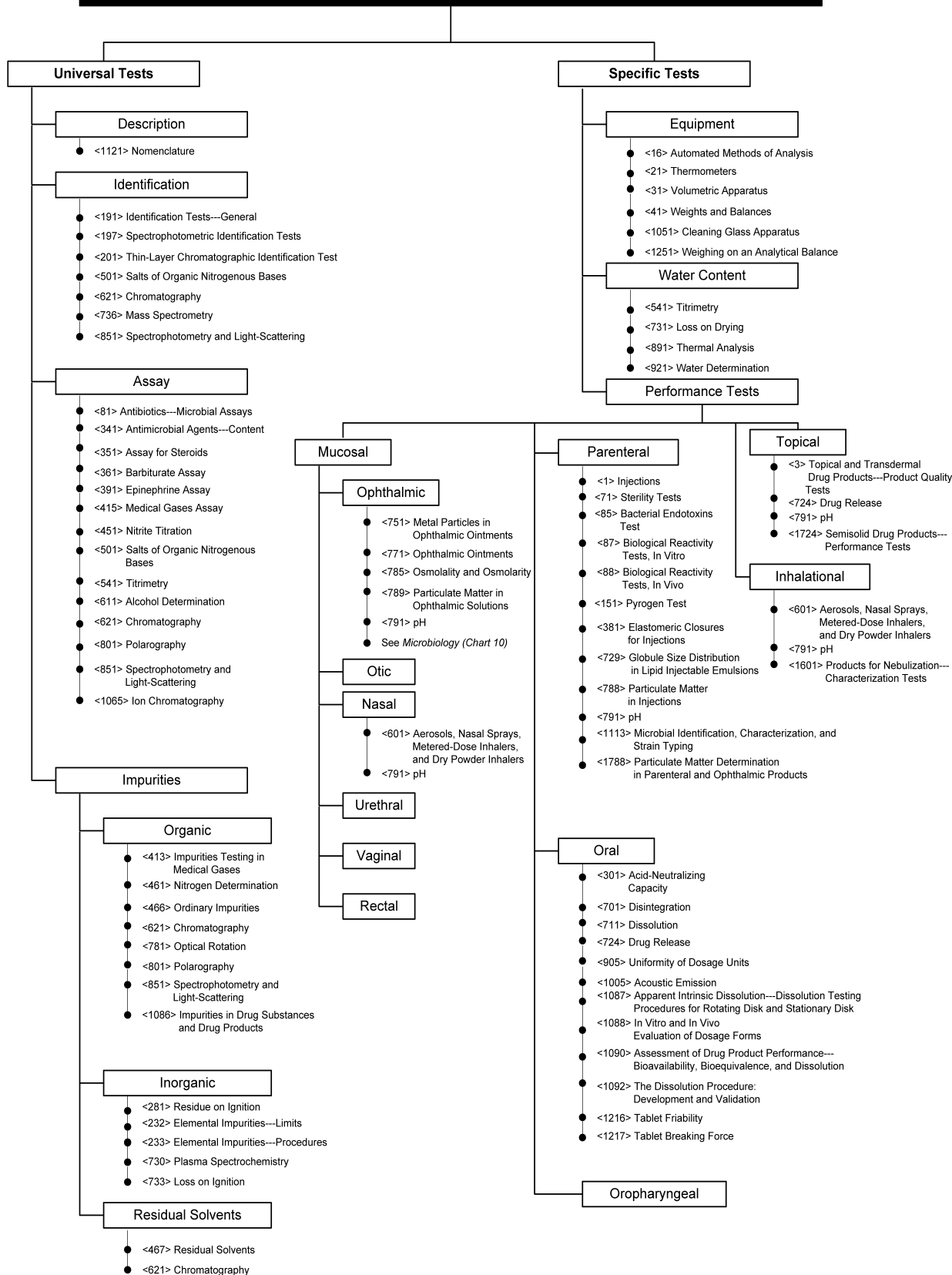


Chart 5. Biotechnology-Derived Drug Products



Chart 6. Vaccines

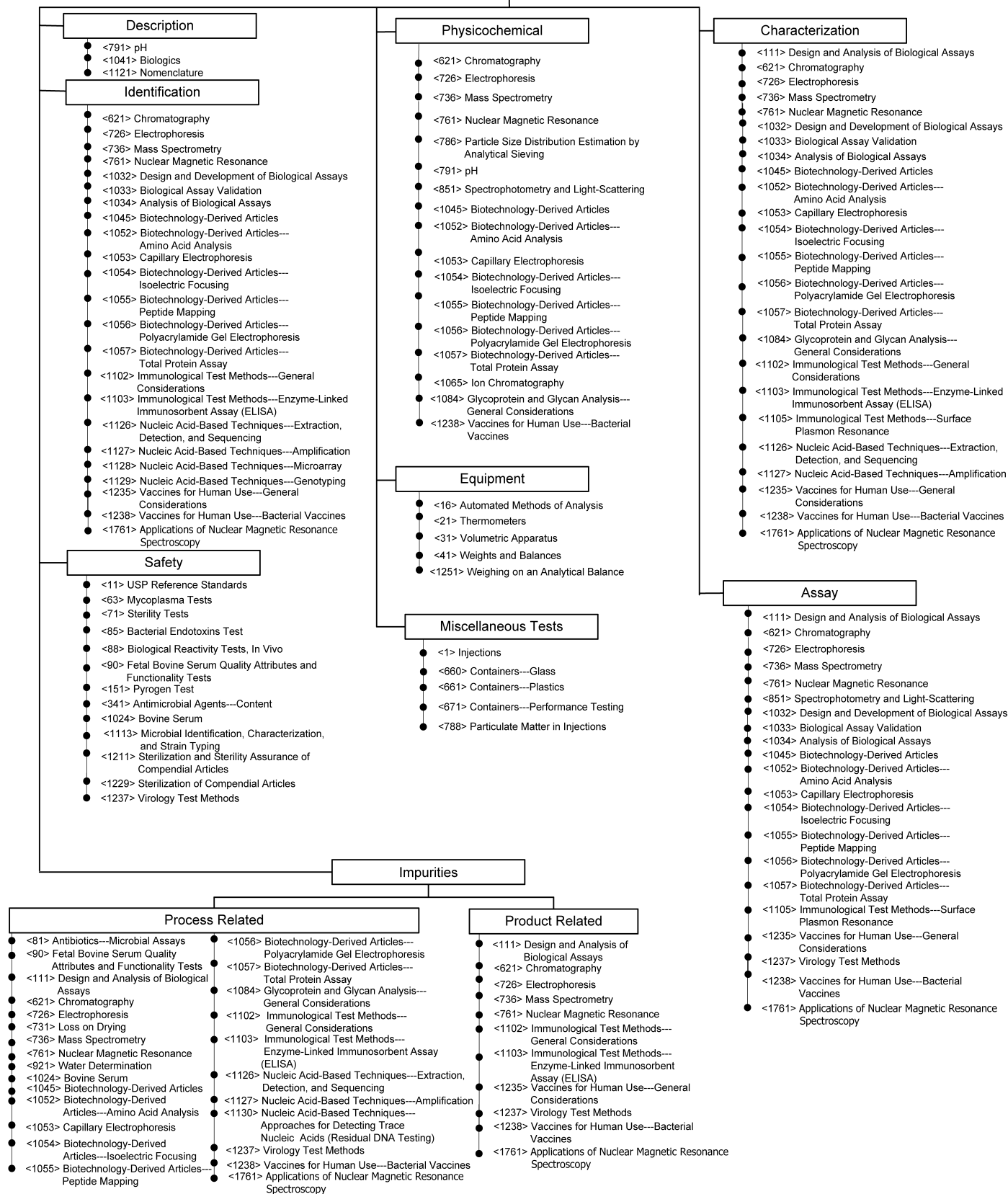


Chart 7. Blood and Blood Products

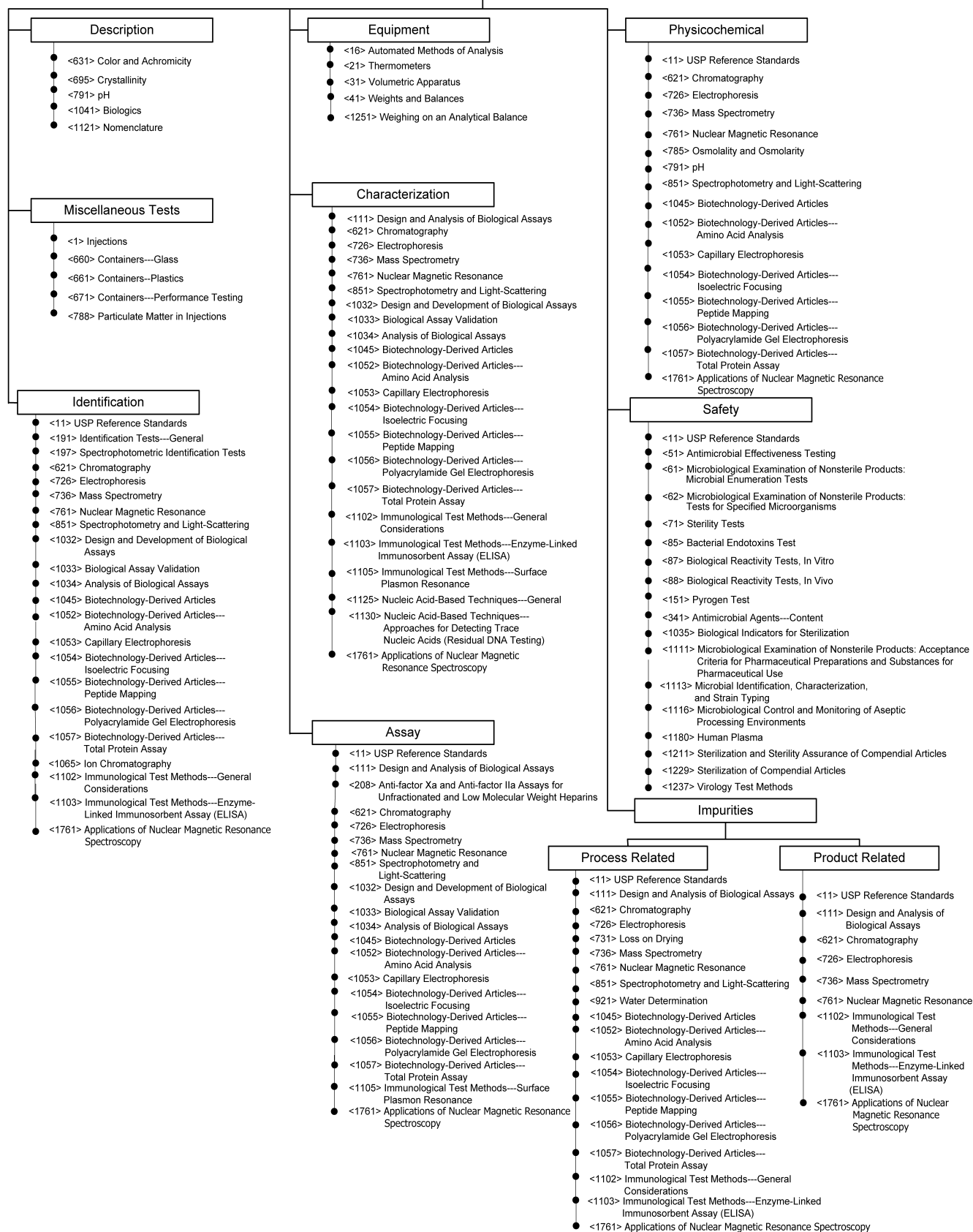


Chart 8. Gene and Cell Therapy Products

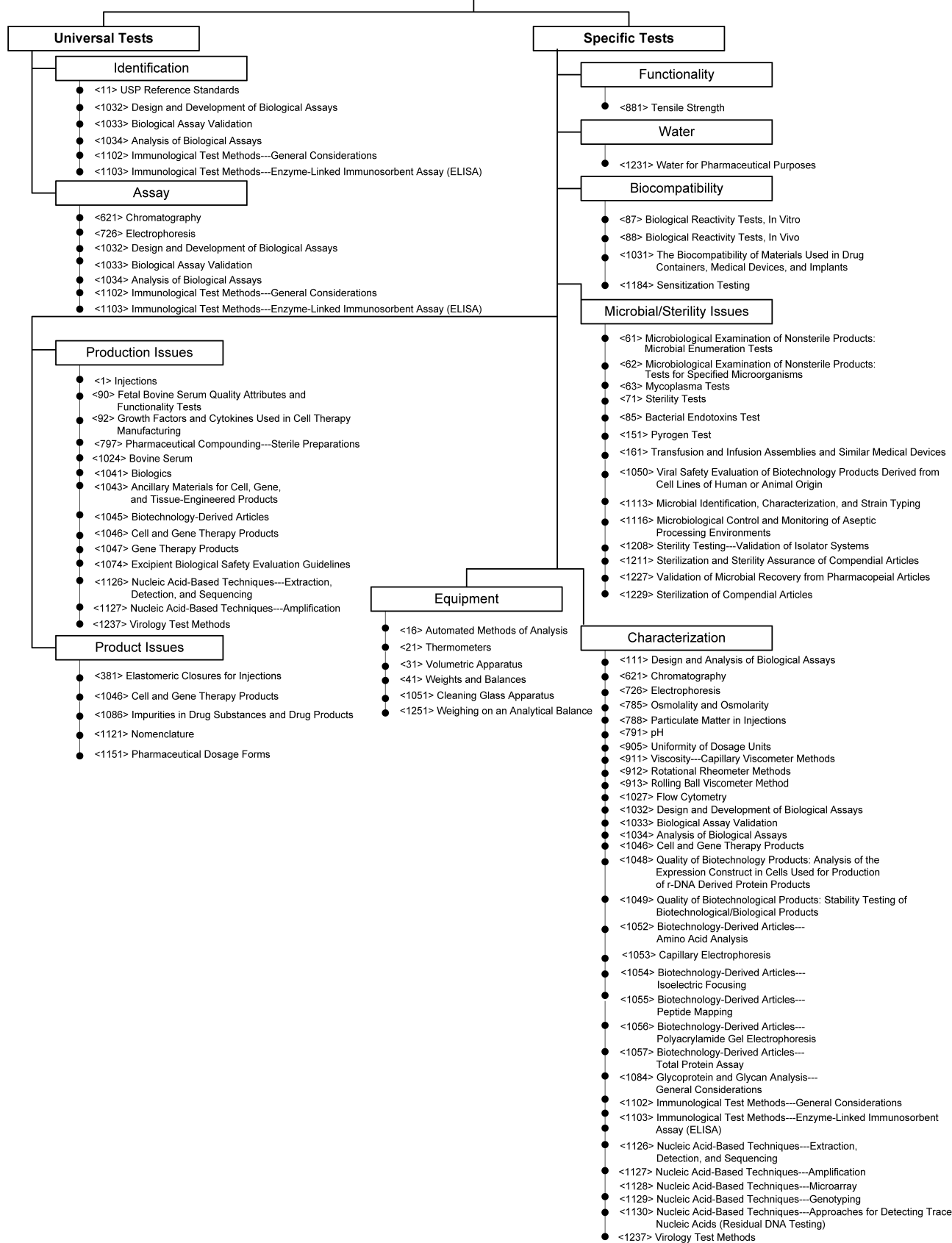


Chart 9. Drug Product Distribution

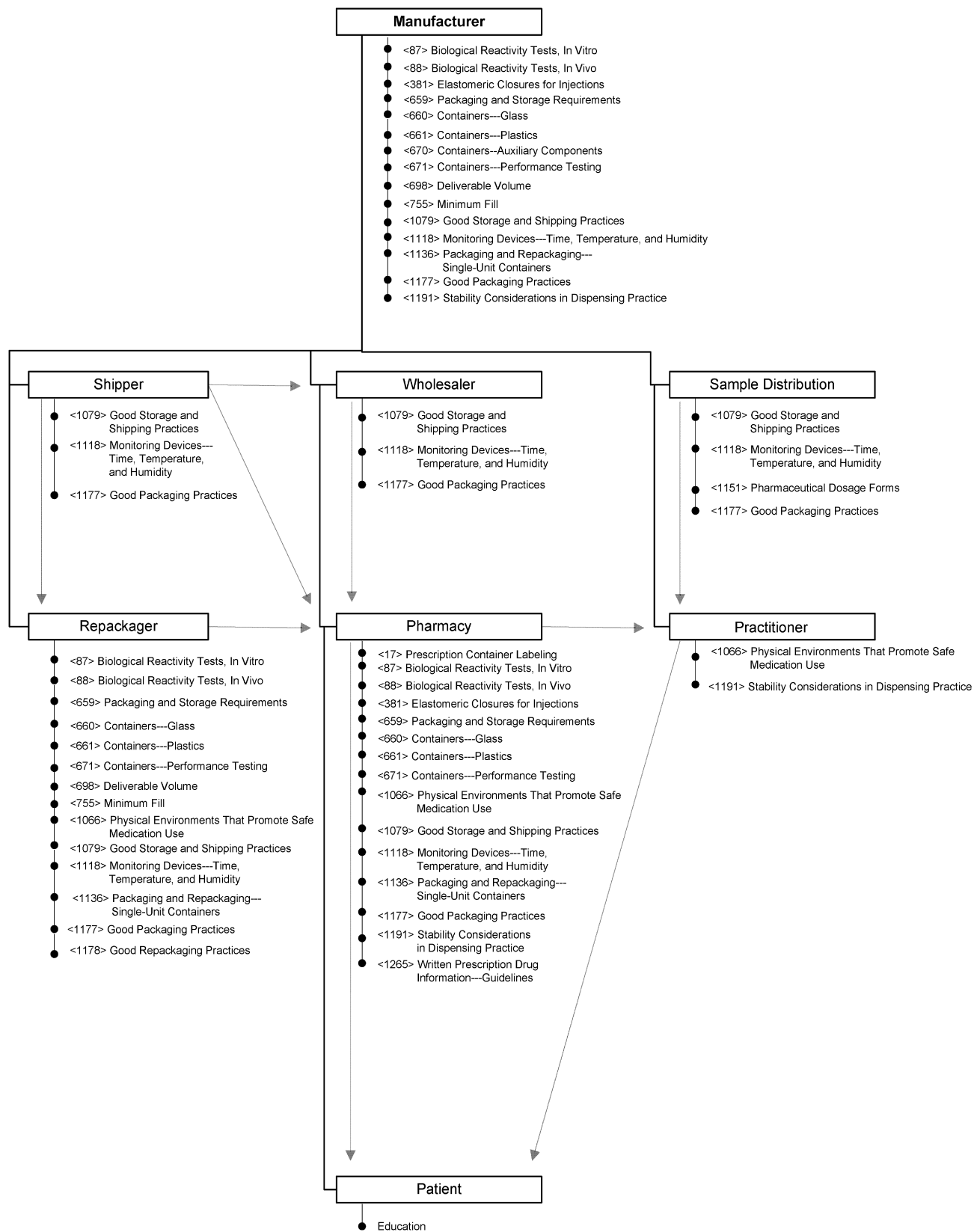


Chart 10. Microbiology

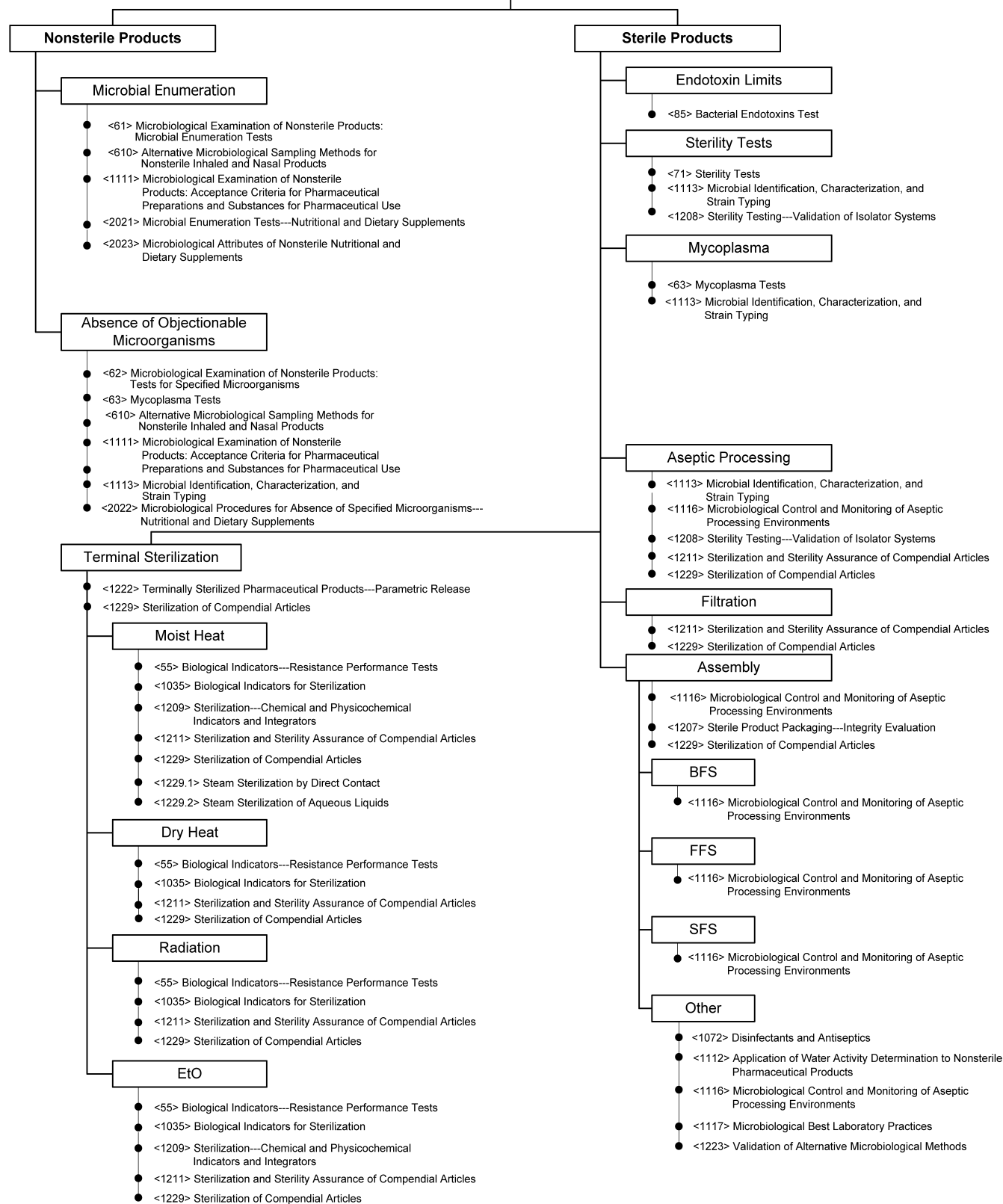


Chart 11. Dietary Supplement Ingredients

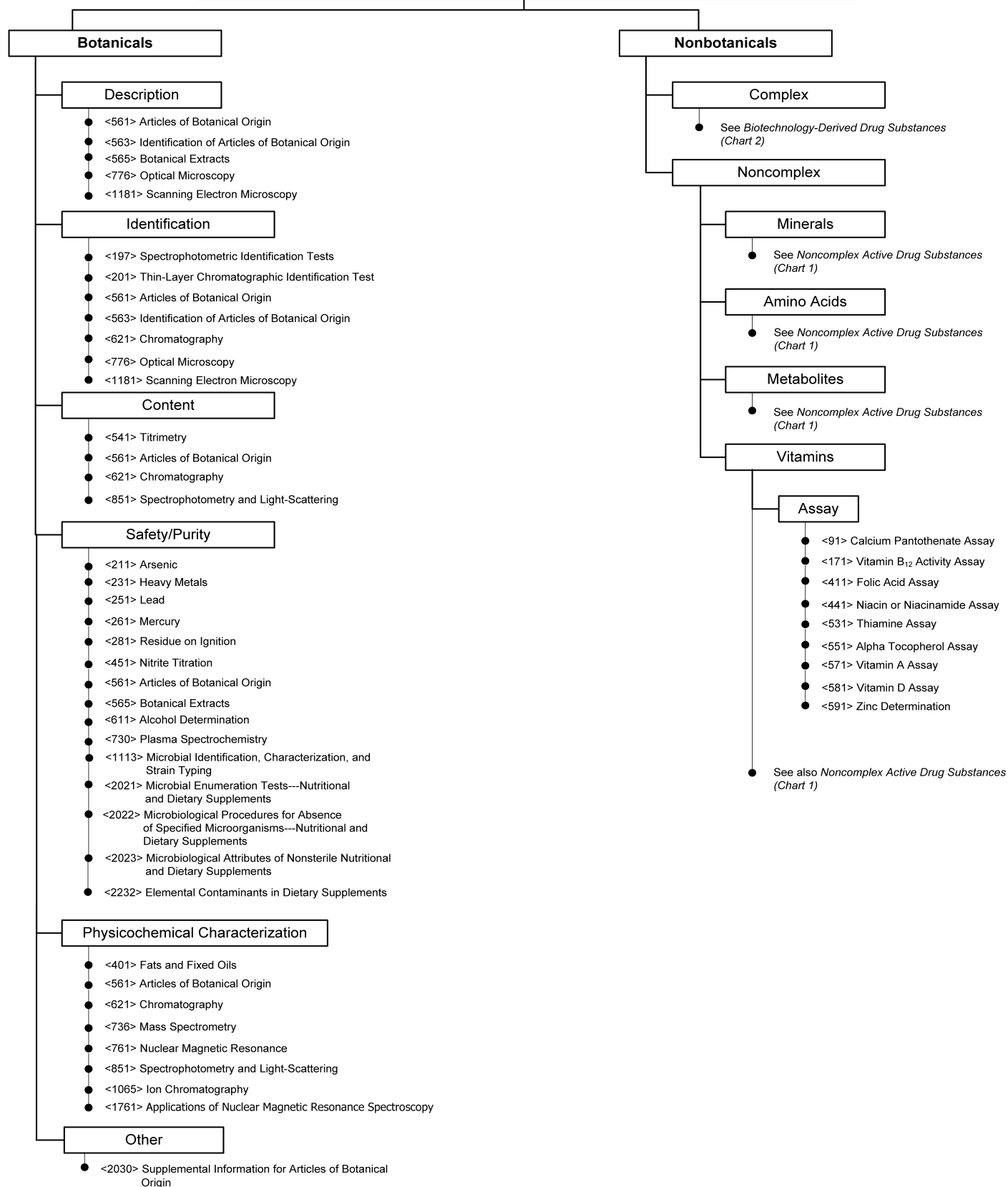
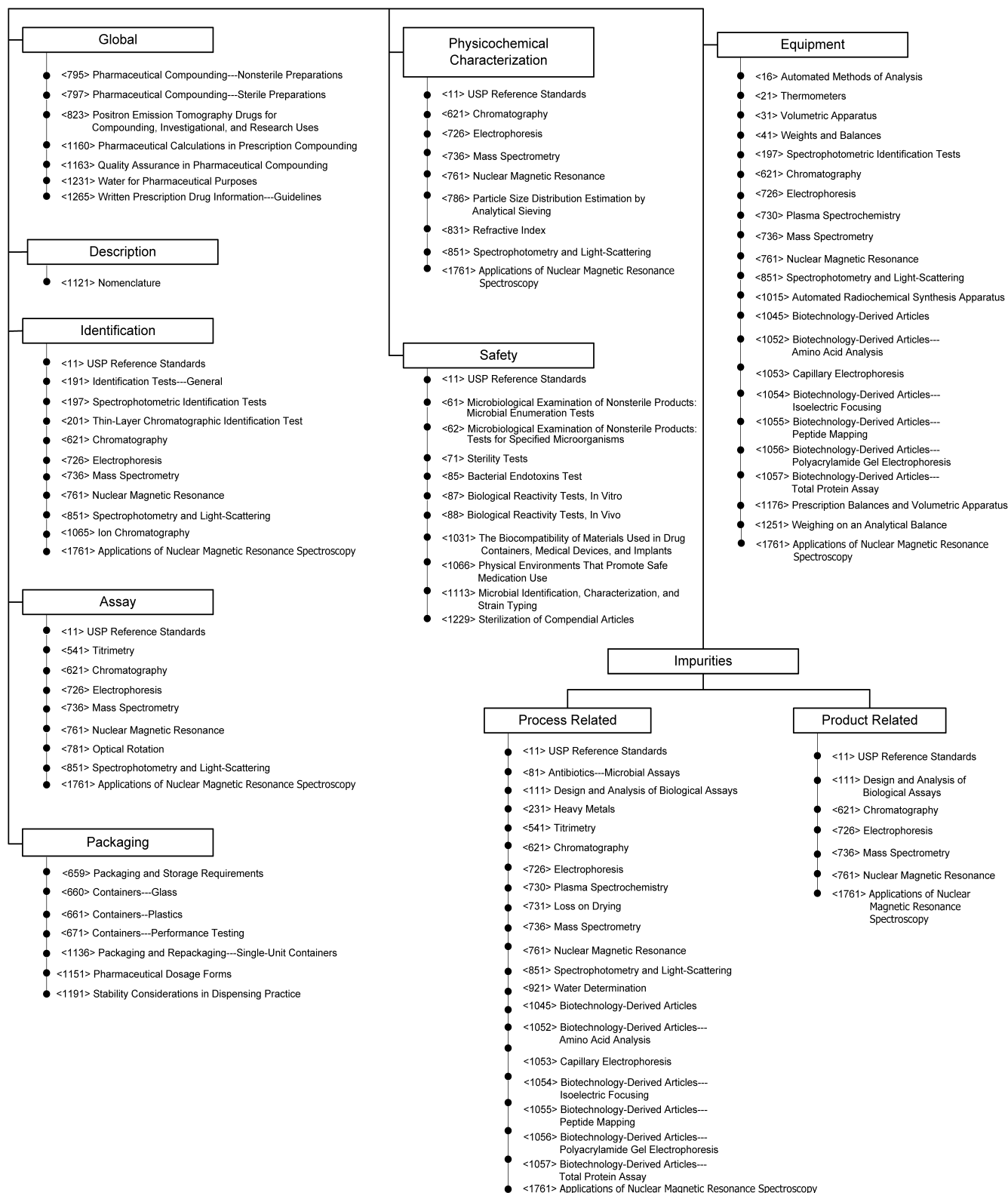


Chart 12. Dietary Supplement Products



Chart 13. Compounding—Substance/Preparation/Practice



General Chapters

General Tests and Assays

Biological Tests and Assays

(87) BIOLOGICAL REACTIVITY TESTS, IN VITRO

Change to read:

The following tests are designed to determine the biological reactivity of mammalian cell cultures following contact with the elastomeric plastics and other polymeric materials with direct or indirect patient contact or of specific extracts prepared from the materials under test. It is essential that the tests be performed on the specified surface area. When the surface area of the specimen cannot be determined, use 0.1 g of elastomer or 0.2 g of plastic or other material for every mL of extraction fluid. Exercise care in the preparation of the materials to prevent contamination with microorganisms and other foreign matter.

Three tests are described (i.e., the *Agar Diffusion Test*, the *Direct Contact Test*, and the *Elution Test*).¹ The decision as to which type of test or the number of tests to be performed to assess the potential biological response of a specific sample or extract depends upon the material, the final product, and its intended use. Other factors that may also affect the suitability of sample for a specific use are the polymeric composition; processing and cleaning procedures; contacting media; inks; adhesives; absorption, adsorption, and permeability of preservatives; and conditions of storage. Evaluation of such factors should be made by appropriate additional specific tests before determining that a product made from a specific material is suitable for its intended use. ■ Materials that fail the *in vitro* tests are candidates for the *in vivo* tests described in *Biological Reactivity Tests, In Vivo* (88).

■1S (USP36)

USP Reference Standards (11)—USP High-Density Polyethylene RS. USP Positive Bioreaction RS.

¹ Further details are given in the following publications of the American Society for Testing and Materials, 1916 Race St., Philadelphia, PA 19103: "Standard Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity," ASTM Designation F 895-84; "Standard Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices," ASTM Designation F 813-83.

Change to read:

Cell Culture Preparation—Prepare multiple cultures of L-929 (ATCC cell line CCL 1, NCTC clone 929■; alternative cell lines obtained from a standard repository may be used with suitable validation■1S (USP36)) mammalian fibroblast cells in serum-supplemented minimum essential medium having a seeding density of about 10^5 cells per mL. Incubate the cultures at $37 \pm 1^\circ$ in a humidified incubator for NLT 24 h in a $5 \pm 1\%$ carbon dioxide atmosphere until a monolayer, with greater than 80% confluence, is obtained. Examine the prepared cultures under a microscope to ensure uniform, near-confluent monolayers. [NOTE—The reproducibility of the *In Vitro Biological Reactivity Tests* depends upon obtaining uniform cell culture density.]

Extraction Solvents—*Sodium Chloride Injection* (see monograph—use Sodium Chloride Injection containing 0.9% of NaCl). Alternatively, serum-free mammalian cell culture media or serum-supplemented mammalian cell culture media may be used. Serum supplementation is used when extraction is done at 37° for 24 h.

Apparatus—

Autoclave—Employ an autoclave capable of maintaining a temperature of $121 \pm 2^\circ$, equipped with a thermometer, a pressure gauge, a vent cock, a rack adequate to accommodate the test containers above the water level, and a water cooling system that will allow for cooling of the test containers to about 20° , but not below 20° , immediately following the heating cycle.

Oven—Use an oven, preferably a mechanical convection model, that will maintain operating temperatures in the range of 50° – 70° within $\pm 2^\circ$.

Incubator—Use an incubator capable of maintaining a temperature of $37 \pm 1^\circ$ and a humidified atmosphere of $5 \pm 1\%$ carbon dioxide in air.

Extraction Containers—Use only containers, such as ampuls or screw-cap culture test tubes, or their equivalent, of Type I glass. If used, culture test tubes, or their equivalent, are closed with a screw cap having a suitable elastomeric liner. The exposed surface of the elastomeric liner is completely protected with an inert solid disk 50–75 μ m in thickness. A suitable disk can be fabricated from polytef.

Preparation of Apparatus—Cleanse all glassware thoroughly with chromic acid cleansing mixture and, if necessary, with hot nitric acid followed by prolonged rinsing with Sterile Water for Injection. Sterilize and dry by a suitable process for containers and devices used for extraction, transfer, or administration of test material. If ethylene oxide is used as the sterilizing agent, allow NLT 48 h for complete degassing.

Procedure—

Preparation of Sample for Extracts—Prepare as directed in the *Procedure* under *Biological Reactivity Tests, In Vivo* (88).

Preparation of Extracts—Prepare as directed for *Preparation of Extracts* in *Biological Reactivity Tests, In Vivo* (88) using

either Sodium Chloride Injection (0.9% NaCl) or serum-free mammalian cell culture media as *Extraction Solvents*. [NOTE—If extraction is done at 37° for 24 h in an incubator, use cell culture media supplemented by serum. The extraction conditions should not in any instance cause physical changes, such as fusion or melting of the material pieces, other than a slight adherence.]

Change to read:

Agar Diffusion Test

This test is designed for elastomeric closures in a variety of shapes. The agar layer acts as a cushion to protect the cells from mechanical damage while allowing the diffusion of leachable chemicals from the polymeric specimens. Extracts of materials that are to be tested are applied to a piece of filter paper.

Sample Preparation—Use extracts prepared as directed, or use portions of the test specimens having flat surfaces NLT 100 mm² in surface area.

Positive Control Preparation—Proceed as directed for *Sample Preparation*.

Negative Control Preparation—Proceed as directed for *Sample Preparation*.

Procedure—Using 7 mL of cell suspension prepared as directed under *Cell Culture Preparation*, prepare the monolayers in plates having a 60-mm diameter. Following incubation, aspirate the culture medium from the monolayers, and replace it with serum-supplemented culture medium containing NMT 2% of agar. [NOTE—The quality of the agar must be adequate to support cell growth. The agar layer must be thin enough to permit diffusion of leached chemicals.] Place the flat surfaces of *Sample Preparation*, *Negative Control Preparation*, and *Positive Control Preparation* or their extracts in an appropriate extracting medium, in duplicate cultures in contact with the solidified agar surface. Use no more than three specimens per prepared plate. Incubate all cultures for NLT 24 h at 37 ± 1°, preferably in a humidified incubator containing 5 ± 1% of carbon dioxide. Examine each culture around each *Sample*, *Negative Control*, and *Positive Control*, under a microscope, using a suitable stain, if desired.

Interpretation of Results—The biological reactivity (cellular degeneration and malformation) is described and rated on a scale of 0–4 (see *Table 1*). Measure the responses of the cell cultures to the *Sample Preparation*, the *Negative Control Preparation*, and the *Positive Control Preparation*. The cell culture test system is suitable if the observed responses to the *Negative Control Preparation* is grade 0 (no reactivity) and to the *Positive Control Preparation* is at least grade 3 (moderate). The *Sample* meets the requirements of the test if the response to the *Sample Preparation* is not greater than grade 2 (mildly reactive). Repeat the procedure if the suitability of the system is not confirmed.

Table 1. Reactivity Grades for Agar Diffusion Test and Direct Contact Test

Grade	Reactivity	Description of Reactivity Zone
0	None	No detectable zone around or under specimen
1	Slight	Some malformed or degenerated cells under specimen
2	Mild	Zone limited to area under specimen and less than 0.45 cm beyond specimen <small>■1S (USP36)</small>
3	Moderate	Zone extends <small>■0.45■1S (USP36)</small> to 1.0 cm beyond specimen
4	Severe	Zone extends greater than 1.0 cm beyond specimen

Change to read:

Direct Contact Test

This test is designed for materials in a variety of shapes. The procedure allows for simultaneous extraction and testing of leachable chemicals from the specimen with a serum-supplemented medium. The procedure is not appropriate for very low- or high-density materials that could cause mechanical damage to the cells.

Sample Preparation—Use portions of the test specimen having flat surfaces NLT 100 mm² in surface area.

Positive Control Preparation—Proceed as directed for *Sample Preparation*.

Negative Control Preparation—Proceed as directed for *Sample Preparation*.

Procedure—Using 2 mL of cell suspension prepared as directed under *Cell Culture Preparation*, prepare the monolayers in plates having a 35-mm diameter. Following incubation, aspirate the culture medium from the cultures, and replace it with 0.8 mL of fresh culture medium. Place a single *Sample Preparation*, a *Negative Control Preparation*, and a *Positive Control Preparation* in each of duplicate cultures. Incubate all cultures for NLT 24 h at 37 ± 1° in a humidified incubator containing 5 ± 1% of carbon dioxide. Examine each culture around each *Sample*, *Negative Control*, and *Positive Control Preparation*, ■1S (USP36) under a microscope, using a suitable stain, if desired.

Interpretation of Results—Proceed as directed for *Interpretation of Results* under *Agar Diffusion Test*. The *Sample* meets the requirements of the test if the response to the *Sample Preparation* is not greater than grade 2 (mildly reactive). Repeat the procedure if the suitability of the system is not confirmed.

Change to read:

Elution Test

This test is designed for the evaluation of extracts of polymeric materials. The procedure allows for extraction of the specimens at physiological or nonphysiological temperatures for varying time intervals. It is appropriate for high-density materials and for dose-response evaluations.

Sample Preparation—Prepare as directed in *Preparation of Extracts*, using either Sodium Chloride Injection (0.9% NaCl) or serum-free mammalian cell culture media as *Extraction Solvents*. If the size of the *Sample* cannot be readily measured, a mass of NLT 0.1 g of elastomeric material or 0.2 g of plastic or polymeric material per mL of extraction medium may be used. Alternatively, use serum-supplemented mammalian cell culture media as the extracting medium to simulate more closely physiological conditions. Prepare the extracts by heating for 24 h in an incubator containing 5 ± 1% of carbon dioxide. Maintain the extraction temperature at 37 ± 1°, because higher temperatures may cause denaturation of serum proteins.

Positive Control Preparation—Proceed as directed for *Sample Preparation*.

Negative Control Preparation—Proceed as directed for *Sample Preparation*.

Procedure—Using 2 mL of cell suspension prepared as directed under *Cell Culture Preparation*, prepare the monolayers in plates having a 35-mm diameter. Following incubation, aspirate the culture medium from the monolayers, and replace it with extracts of the *Sample Preparation*, *Negative Control Preparation*, or *Positive Control Preparation*. The se-

rum-supplemented and serum-free cell culture media extracts are tested in duplicate without dilution (100%). The Sodium Chloride Injection extract is diluted with serum-supplemented cell culture medium and tested in duplicate at 25% extract concentration. Incubate all cultures for 48 h at 37 ± 1° in a humidified incubator preferably containing 5 ± 1% of carbon dioxide. Examine each culture at 48 h, under a microscope, using a suitable stain, if desired.

Interpretation of Results—Proceed as directed for *Interpretation of Results* under *Agar Diffusion Test* but use *Table 2*. The *Sample* meets the requirements of the test if the response to the *Sample Preparation* is not greater than grade 2 (mildly reactive). Repeat the procedure if the suitability of the system is not confirmed. For dose-response evaluations, repeat the procedure, using quantitative dilutions of the sample extract.

Table 2. Reactivity Grades for Elution Test		
Grade	Reactivity	Conditions of All Cultures
0	None	Discrete intracytoplasmic granules; no cell lysis
1	Slight	■Less than or equal to ■15 (USP36) 20% of the cells are round, loosely attached, and without intracytoplasmic granules; occasional lysed cells are present
2	Mild	■Greater than 20% to less than or equal to ■15 (USP36) 50% of the cells are round and devoid of intracytoplasmic granules; no extensive cell lysis and empty areas between cells
3	Moderate	■Greater than 50% to less than ■15 (USP36) 70% of the cell layers contain rounded cells or are lysed
4	Severe	Nearly complete destruction of the cell layers

(88) BIOLOGICAL REACTIVITY TESTS, IN VIVO

Change to read:

The following tests are designed to determine the biological response of animals to elastomers, plastics, and other polymeric material with direct or indirect patient contact, or by the injection of specific extracts prepared from the material under test. It is essential to make available the specific surface area for extraction. When the surface area of the specimen cannot be determined, use 0.1 g of elastomer or 0.2 g of plastic or other material for every mL of extraction fluid. Also, it is essential to exercise care in the preparation of the materials to be injected or instilled to prevent contamination with microorganisms and other foreign matter. Three tests are described. The *Systemic Injection Test* and the *Intracutaneous Test* are used for elastomeric materials, especially to elastomeric closures for which the appropriate *Biological Reactivity Tests, In Vitro* (87) have indicated significant biological reactivity. These two tests are used for plastics and **■and ■15 (USP36)** other polymers, in addition to a third test, the *Implantation Test*, to test the suitability of these materials

intended for use in fabricating containers and accessories thereto, for use in parenteral preparations, and for use in medical devices, implants, and other systems.

These three tests are applied to materials or medical devices, if there is a need for classification of plastics and other polymers based on in vivo biological reactivity testing.

For the purpose of this chapter, these definitions apply: the *Sample* is the specimen under test or an extract prepared from such a specimen. A *Blank* consists of the same quantity of the same extracting medium that is used for the extraction of the specimen under test, treated in the same manner as the extracting medium containing the specimen under test. A *Negative Control*¹ is a specimen that gives no reaction under the conditions of the test.

Change to read:

CLASSIFICATION OF PLASTICS

Six Plastic Classes are defined (see *Table 1*). This classification is based on responses to a series of in vivo tests for which extracts, materials, and routes of administration are specified. These tests are directly related to the intended end-use of the plastic articles. The choice of extractants is representative of the vehicles in preparations with which the plastics are likely to be in contact. The *Table 1* classification facilitates communication among suppliers, users, and manufacturers of plastics by summarizing the tests to be performed for containers for injections and medical devices if a need for classification exists.

With the exception of the *Implantation Test*, the procedures are based on the use of extracts that, depending on the heat resistance of the material, are prepared at one of three standard temperatures: 50°, 70°, and 121°. Therefore, the class designation of a plastic must be accompanied by an indication of the temperature of extraction (e.g., IV-121°, which represents a class IV plastic extracted at 121°, or I-50°, which represents a class I plastic extracted at 50°).

Plastics may be classified as USP Plastic Classes I–VI only on the basis of the response criteria prescribed in *Table 1*.

This classification does not apply to plastics that are intended for use as containers for oral or topical products, or that may be used as an integral part of a drug formulation. *Table 1* does not apply to natural elastomers, which are to be tested in Sodium Chloride Injection and vegetable oils only.

The *Systemic Injection Test* and the *Intracutaneous Test* are designed to determine the systemic and local, respectively, biological responses of animals to plastics and other polymers by the single-dose injection of specific extracts prepared from a *Sample*. The *Implantation Test* is designed to evaluate the reaction of living tissue to the plastic and other polymers by the implantation of the *Sample* itself into animal tissue. The proper preparation and placement of the specimens under aseptic conditions are important in the conduct of the *Implantation Test*.

These tests are designed for application to plastics and other polymers in the condition in which they are used. If the material is to be exposed to any cleansing or sterilization process prior to its end-use, then the tests are to be conducted on a *Sample* prepared from a specimen preconditioned by the same processing.

Factors such as material composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a material for a specific use. Evaluation of such factors should be made by appropriate additional specific tests to determine the suitability of a material for its intended use.

¹ USP High-Density Polyethylene RS.

Table 1. Classification of Plastics

Plastic Classes ^a						Tests to be Conducted			
I	II	III	IV	V	VI	Test Material	Animal	Dose	Procedure ^b
x	x	x	x	x	x	Extract of Sample in Sodium Chloride Injection	Mouse	50 mL/kg	A ■(IV)■1S (USP36)
x	x	x	x	x	x		■Rabbit or Guinea Pig■1S (USP36)	0.2 mL/animal at each of ■10 or 6■1S (USP36) sites	B ■(IC)■1S (USP36)
	x	x	x	x	x		Mouse	50 mL/kg	A ■(IP)■1S (USP36)
	x	x	x	x	x	Extract of Sample in 1 in 20 Solution of Alcohol in Sodium Chloride Injection	■Rabbit or Guinea Pig■1S (USP36)	0.2 mL/animal at each of ■10 or 6■1S (USP36) sites	B ■(IC)■1S (USP36)
		x		x	x	Extract of Sample in Polyethylene Glycol 400	Mouse	10 g/kg	A (IP)
				x	x		■Rabbit or Guinea Pig■1S (USP36)	0.2 mL/animal at each of ■10 or 6■1S (USP36) sites	B ■(IC)■1S (USP36)
		x	x	x	x		Mouse	50 mL/kg	A (IP)
			x	x	x	Extract of Sample in Vegetable Oil	■Rabbit or Guinea Pig■1S (USP36)	0.2 mL/animal at each of ■10 or 6■1S (USP36) sites	B ■(IC)■1S (USP36)
			x		x	Implant strips of Sample	Rabbit	4 strips/animal	C
			x		x	Implant Sample	Rat	2 Samples/animal	C

^aTests required for each class are indicated by “x” in appropriate columns.

^bLegend: A (IP)—Systemic Injection Test (intraperitoneal); B (IC)—Intracutaneous Test (intracutaneous); C—Implantation Test (intramuscular or subcutaneous implantation).

USP Reference Standards (11)—USP High-Density Polyethylene RS.

Change to read:

Extracting Media—

SODIUM CHLORIDE INJECTION (see monograph). Use Sodium Chloride Injection containing 0.9% of NaCl.

1 IN 20 SOLUTION OF ALCOHOL IN SODIUM CHLORIDE INJECTION. POLYETHYLENE GLYCOL 400 (see monograph).

VEGETABLE OIL— Use freshly refined Sesame Oil (see monograph) or Cottonseed Oil (see monograph) or other suitable vegetable oils.

DRUG PRODUCT VEHICLE (where applicable).

WATER FOR INJECTION (see monograph).

NOTE—The Sesame Oil or Cottonseed Oil or other suitable vegetable oil meets the following additional requirements. Obtain, if possible, freshly refined oil. Use three properly prepared animals, and inject the oil intracutaneously in a dose of 0.2 mL into each of 10 sites per animal, and observe the animals at 24, 48, and 72 h following injection. Rate the observations at each site on the numerical scale indicated in Table 2. For the 3 ■rabbits or guinea pigs (30 or 18■1S (USP36) injection sites), at any observation time, the average response for erythema is not greater than 0.5 and for edema is not greater than 1.0, and no site shows a tissue reaction larger than 10 mm in overall diameter. The residue of oil at the injection site should not be misinterpreted as edema. Edematous tissue blanches when gentle pressure is applied.

Table 2. Evaluation of Skin Reactions ■■1S (USP36)

Erythema and Eschar Formation	Score
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet-redness) to slight eschar formation (injuries in depth)	4
Edema Formation ^b	Score
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4

■^a Draize JH, Woodward G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J Pharmacol Exp Ther* 1944;82:377–390.

■1S (USP36)

^b Excludes noninflammatory (mechanical) edema from the blank or extraction fluid.

Apparatus—The apparatus for the tests includes the following.

AUTOClave—Use an autoclave capable of maintaining a temperature of $121 \pm 2.0^\circ$, equipped with a thermometer, a pressure gauge, a vent cock, a rack adequate to accommodate the test containers above the water level, and a water cooling system that will allow for cooling of the test containers to about, but not below, 20° immediately following the heating cycle.

OVEN—Use an oven, preferably a forced-circulation model, that will maintain operating temperatures of 50° or 70° within ±2°.

EXTRACTION CONTAINERS—Use only containers, such as ampuls or screw-cap culture test tubes, of Type I glass. If used, culture test tubes are closed with screw caps having suitable elastomeric liners. The exposed surface of the elastomeric liner is completely protected with an inert solid disk 0.05–0.075 mm in thickness. A suitable disk may be fabricated from a polytef resin.

Preparation of Apparatus—Cleanse all glassware thoroughly with chromic acid cleansing mixture, or if necessary, with hot nitric acid, followed by prolonged rinsing with water. Clean cutting utensils by an appropriate method (e.g., successive cleaning with acetone and methylene chloride) prior to use in subdividing a specimen. Clean all other equipment by thorough scrubbing with a suitable detergent and prolonged rinsing with water.

Render containers and equipment used for extraction, and in transfer and administration of test material, sterile and dry by a suitable process. [NOTE—If ethylene oxide is used as the sterilizing agent, allow adequate time for complete degassing.]

Procedure—

PREPARATION OF SAMPLE—Both the *Systemic Injection Test* and the *Intracutaneous Test* may be performed using the same extract, if desired, or separate extracts may be made for each test. Select and subdivide into portions a *Sample* of the size indicated in Table 3. Remove particulate matter, such as lint and free particles, by treating each subdivided *Sample* or *Negative Control* as follows. Place the *Sample* into a clean, glass-stoppered, 100-mL graduated cylinder of Type I glass, and add about 70 mL of *Water for Injection*. Agitate

for about 30 s, and drain off the water. Repeat this step, and dry those pieces prepared for the extraction with *Vegetable Oil* in an oven at a temperature not exceeding 50°. [NOTE—Do not clean the *Sample* with a dry or wet cloth or by rinsing or washing with an organic solvent, surfactant, etc.]

PREPARATION OF EXTRACTS—Place a properly prepared *Sample* to be tested in an extraction container, and add 20 mL of the appropriate extracting medium. Repeat these directions for each extracting medium required for testing. Also, prepare one 20-mL blank of each medium for parallel injections and comparisons. Extract by heating in an autoclave at 121° for 60 min, in an oven at 70° for 24 h, or at 50° for 72 h. Allow adequate time for the liquid within the container to reach the extraction temperature. [NOTE—The extraction conditions should not in any instance cause physical changes such as fusion or melting of the *Sample* pieces, which result in a decrease in the available surface area. A slight adherence of the pieces can be tolerated. Always add the cleaned pieces individually to the extracting medium. If culture tubes are used for autoclave extractions with *Vegetable Oil*, seal screw caps adequately with pressure-sensitive tape.]

Cool to about room temperature but not below 20°, shake vigorously for several minutes, and decant each extract immediately, using aseptic precautions, into a dry, sterile vessel. Store the extracts at a temperature of 20°–30°, and do not use for tests after 24 h. Of importance are the contact of the extracting medium with the available surface area of the plastic and the time and temperature during extraction, the proper cooling, agitation, and decanting process, and the aseptic handling and storage of the extracts following extraction.

Table 3. Surface Area of Specimen To Be Used^a

Form of Material	Thickness	Amount of Sample for each 20 mL of Extracting Medium	Subdivided into
Film or sheet	<0.5 mm	Equivalent of 120 cm ² total surface area (both sides combined)	Strips of about 5 × 0.3 cm
	0.5–1 mm	Equivalent of 60 cm ² total surface area (both sides combined)	
Tubing	<0.5 mm (wall)	Length (in cm) = 120 cm ² /(sum of ID and OD circumferences)	Sections of about 5 × 0.3 cm
	0.5–1 mm (wall)	Length (in cm) = 60 cm ² /(sum of ID and OD circumferences)	
Slabs, tubing, and molded items	>1 mm	Equivalent of 60 cm ² total surface area (all exposed surfaces combined)	Pieces up to about 5 × 0.3 cm
Elastomers	>1 mm	Equivalent of 25 cm ² total surface area (all exposed surfaces combined)	Do not subdivide ^b

^a When surface area cannot be determined due to the configuration of the specimen, use 0.1 g of elastomer or 0.2 g of plastic or other polymers for every 1 mL of extracting fluid.
^b Molded elastomeric closures are tested intact.

Change to read:

SYSTEMIC INJECTION TEST

This test is designed to evaluate systemic responses to the extracts of materials under test following injection into mice. ■Alternate routes of injection may be used with justification.

■1S (USP36)

Test Animals—Use healthy, not previously used albino mice weighing 17–23 g. For each test group use only mice of the same source. Allow water and food, commonly used for laboratory animals and of known composition, ad libitum.

Procedure—[NOTE—Agitate each extract vigorously prior to withdrawal of injection doses to ensure even distribution of the extracted matter.] Inject each of the five mice in a test group with the *Sample* or the *Blank* as outlined in Table 4, except to dilute each g of the extract of the *Sample* prepared with *Polyethylene Glycol 400*, and the corresponding *Blank*, with 4.1 volumes of *Sodium Chloride Injection* to obtain a solution having a concentration of about 200 mg of polyethylene glycol per mL.

Table 4. Injection Procedure—Systemic Injection Test

Extract or Blank	Dose per kg	Route ^a	■1S (USP36)
Sodium Chloride Injection	50 mL	■IV■1S (USP36)	■1S (USP36)
1 in 20 solution of Alcohol in Sodium Chloride Injection	50 mL	■IV■1S (USP36)	■1S (USP36)
Polyethylene Glycol 400	10 g	IP	—
Drug product vehicle (where applicable)	50 mL	■IV■1S (USP36)	■1S (USP36)
	50 mL	IP	—
Vegetable Oil	50 mL	IP	—

^a IV = intravenous (aqueous sample and blank); IP = intraperitoneal (oleaginous sample and blank).

Observe the animals immediately after injection, again 4 h after injection, and then at least at 24, 48, and 72 h. If during the observation period none of the animals treated with the extract of the *Sample* shows a significantly greater biological reactivity than the animals treated with the *Blank*, the *Sample* meets the requirements of this test. If two or more mice die, or if abnormal behavior such as convulsions or prostration occurs in two or more mice, or if a body weight loss greater than 2 g occurs in three or more mice, the *Sample* does not meet the requirements of the test. If any animals treated with the *Sample* show only slight signs of biological reactivity, and not more than one animal shows gross symptoms of biological reactivity or dies, repeat the test using groups of 10 mice. On the repeat test, all 10 animals treated with the *Sample* show no significant biological reactivity above the *Blank* animals during the observation period.

Change to read:

INTRACUTANEOUS TEST

This test is designed to evaluate local responses to the extracts of materials under test following intracutaneous injection into ■rabbits or guinea pigs.■1S (USP36)

Test Animals—Select healthy, ■rabbits or guinea pigs■1S (USP36) with fur that can be clipped closely and skin

that is free from mechanical irritation or trauma. In handling the animals, avoid touching the injection sites during observation periods, except to discriminate between edema and an oil residue. ■1S (USP36)

Procedure—[NOTE—Agitate each extract vigorously prior to withdrawal of injection doses to ensure even distribution of the extracted matter.] On the day of the test, closely clip the fur on the animal's back on both sides of the spinal column over a sufficiently large test area. Avoid mechanical irritation and trauma. Remove loose hair by means of vacuum. If necessary, swab the skin lightly with diluted alcohol, and dry the skin prior to injection. More than one extract from a given material can be used per ■rabbit or guinea pig,■1S (USP36) if it is determined that the test results will not be affected. For each *Sample* use two animals and inject each intracutaneously, using one side of the animal for the *Sample* and the other side for the *Blank*, as outlined in Table 5. [NOTE—Dilute each g of the extract of the *Sample* prepared with *Polyethylene Glycol 400*, and the corresponding *Blank*, with 7.4 volumes of *Sodium Chloride Injection* to obtain a solution having a concentration of about 120 mg of polyethylene glycol per mL.]

Table 5. Intracutaneous Test

Extract or Blank	Number of Sites (per animal)	Dose (μL per site)
Sample	5	200
Blank	5	200

Examine injection sites for evidence of any tissue reaction such as erythema, edema, and necrosis. Swab the skin lightly, if necessary, with diluted alcohol to facilitate reading of injection sites. Observe all animals at 24, 48, and 72 h after injection. Rate the observations on a numerical scale for the extract of the *Sample* and for the *Blank*, using Table 2. Reclip the fur as necessary during the observation period. The average erythema and edema scores for *Sample* and *Blank* sites are determined at every scoring interval (24, 48, and 72 h) for each ■rabbit or guinea pig.■1S (USP36) After the 72-hour scoring, all erythema scores plus edema scores are totalled separately for each *Sample* and *Blank*. Divide each of the totals by 12 (2 animals × 3 scoring periods × 2 scoring categories) to determine the overall mean score for each *Sample* versus each corresponding *Blank*. The requirements of the test are met if the difference between the *Sample* and the *Blank* mean score is 1.0 or less. If at any observation period the average reaction to the *Sample* is questionably greater than the average reaction to the *Blank*, repeat the test using three additional ■rabbits or guinea pigs.■1S (USP36) The requirements of the test are met if the difference between the *Sample* and the *Blank* mean score is 1.0 or less.

Change to read:

IMPLANTATION TEST

The implantation test is designed for the evaluation of plastic materials and other polymeric materials in direct contact with living tissue. Of importance are the proper preparation of the implant strips and their proper implantation under aseptic conditions. The intramuscular implantation test requires healthy adult ■New Zealand■1S (USP36) rabbits. The test specimens are placed into needles as the delivery system for implantation. Although most materials lend themselves readily to this method, there are a number of materials that are unsuitable for intramuscular implantation. For materials with physical characteristics unsuitable for routine intramuscular implantation, the subcutaneous rat implantation model is a viable alternative.

Intramuscular Implantation in Rabbits

Prepare for implantation 8 strips of the *Sample* and 4 strips of USP High-Density Polyethylene RS. Each strip should measure not less than 10 × 1 mm. The edges of the strips should be as smooth as possible to avoid additional mechanical trauma upon implantation. Strips of the specified minimum size are implanted by means of a hypodermic needle (15–19 gauge) with intravenous point and a sterile trocar. Use either presterilized needles into which the sterile plastic strips are aseptically inserted, or insert each clean strip into a needle, the cannula and hub of which are protected with an appropriate cover, and then subjected to the appropriate sterilization procedure. [NOTE—Allow for proper degassing if agents such as ethylene oxide are used.]

Test Animals—Select healthy, adult rabbits weighing not less than 2.5 kg, and with paravertebral muscles that are sufficiently large in size to allow for implantation of the test strips. Do not use any muscular tissue other than the paravertebral site. The animals must be anesthetized with a commonly used anesthetic agent to a degree deep enough to prevent muscular movements, such as twitching. ■See the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) guidelines. ■1S (USP36)

Procedure—Perform the test in a clean area. On the day of the test or up to 20 h before testing, clip the fur of the animals on both sides of the spinal column. Remove loose hair by means of vacuum. Swab the skin lightly with diluted alcohol, and dry the skin prior to injection.

Implant four strips of the *Sample* into the paravertebral muscle on one side of the spine of each of two rabbits, 2.5–5 cm from the midline and parallel to the spinal column, and about 2.5 cm apart from each other. In a similar fashion implant two strips of USP High-Density Polyethylene RS in the opposite muscle of each animal. Insert a sterile stylet into the needle to hold the implant strip in the tissue while withdrawing the needle. If excessive bleeding is observed after implantation of a strip, place a duplicate strip at another site.

Keep the animals for a period of not less than 120 h, and sacrifice them at the end of the observation period by administering an overdose of an anesthetic agent or other suitable agents. Allow sufficient time to elapse for the tissue to be cut without bleeding. Examine macroscopically the area of the tissue surrounding the center portion of each implant strip. Use a magnifying lens and auxiliary light source. Observe the *Sample* and *Control* implant sites for hemorrhage, necrosis, discolorations, and infections, and record the observations. Measure encapsulation, if present, by recording the width of the capsule (from the periphery of the space occupied by the implant *Control* or *Sample* to the periphery of the capsule) rounded to the nearest 0.1 mm. Score encapsulation according to *Table 6*.

Table 6. Evaluation of Encapsulation in the Implantation Test

Capsule Width	Score
None	0
Up to 0.5 mm	1
0.6–1.0 mm	2
1.1–2.0 mm	3
Greater than 2.0 mm	4

Calculate the differences between average scores for the *Sample* and *Control* sites. The requirements of the test are met if the difference does not exceed 1.0, or if the difference between the *Sample* and *Control* mean scores for more than one of the four implant sites does not exceed 1 for any implanted animal.

Subcutaneous Implantation in Rats

Prepare for implantation 10 sample specimens and 10 control specimens. The size and shape of the control specimens shall be as similar to that of the test specimens as practically possible. For example, specimens made of sheeting material shall be 10–12 mm in diameter and from 0.3–1 mm in thickness. The edges of the specimens should be as smooth as possible to avoid additional mechanical trauma upon implantation.

Test Animals—Select healthy ■albino ■1S (USP36) rats weighing 225–350 g at the time of implantation.

Procedure—Perform the test in a clean area. Anesthetize ■(see AAALAC guidelines) ■1S (USP36) the animal until a surgical plane is achieved. Clip the fur of the animals on both sides of the spinal column. Remove loose hair by means of vacuum. Clean the clipped area with povidone–iodine solution. Using aseptic technique, make two midline incisions (approximately 1.0 cm long) through the skin at the cranial and caudal regions on the dorsal surface. Using blunt dissection, separate the fascia connecting skin to muscle to form a pocket underneath the skin lateral to each side of the incision (base of pocket approximately 20 mm from the line of implant). Insert a sterile sample into each pocket, and close the incision with wound clips or sutures. Implant two test samples and two control samples in each of five rats. Keep the animals for a period of at least seven days, and sacrifice them at the end of the observation period by CO₂ induced hypoxia or administering an overdose of an anesthetic agent. Allow sufficient time to elapse for the tissue to be cut without bleeding. Cut the skin (dorsal surface) longitudinally and lay back. Carefully examine macroscopically the area of the tissue surrounding the implant. Cut the sample in half and remove for close examination of the tissue in direct contact with the sample. Use a magnifying lens and auxiliary light source, if appropriate. Observe the *Sample* and *Control* implant sites for hemorrhage, necrosis, discolorations, and infections, and record the observations. Measure encapsulation, if present, by recording the width of the capsule (from the periphery of the space occupied by the implant *Control* or *Sample* to the periphery of the capsule) rounded to the nearest 0.1 mm. Score encapsulation according to *Table 6*. Calculate the differences between average scores for the *Sample* and *Control* sites. The requirements of the test are met if the difference does not exceed 1.0.

Change to read:

SAFETY TESTS—BIOLOGICALS

The safety test set forth here is intended to detect in an article any unexpected, unacceptable biological reactivity. This in vivo test is provided for the safety assessment of ■1S (USP36) biotechnology-derived products.

Safety Test

Select five healthy mice not previously used for testing, weighing 17–23 g, unless otherwise directed in the individual monograph or elsewhere in this chapter, and maintained on an adequate balanced diet. Prepare a test solution as directed in the individual monograph. Unless otherwise directed in the individual monograph or elsewhere in this chapter, inject a dose of 0.5 mL of the test solution into each of the mice, using a 26-gauge needle of suitable length, or of the length specified below as applicable. Observe the animals over the 48 h following the injection. If, at the end of 48 h, all of the animals survive and not more than one of the animals shows outward symptoms of a re-

action not normally expected of the level of toxicity related to the article, the requirements of this test are met. If one or more animals die or if more than one of the animals shows signs of abnormal or untoward toxicity of the article under test, repeat the test using at least another 10 mice similar to those used in the initial test, but weighing 20 ± 1 g. In either case, if all of the animals survive for 48 h and show no symptoms of a reaction indicative of an abnormal or undue level of toxicity of the article, the requirements of the test are met. ■Body weights of mice before and at the end of the test should be obtained to detect any untoward effects. Animals that show signs of toxicity should be grossly necropsied and subjected to histopathology if necessary.

■1S (USP36)

For biologics, perform the test according to the procedures prescribed in the *Code of Federal Regulations*,

■1S (USP36) Section 610.11. ■1S (USP36)

Chemical Tests and Assays

LIMIT TESTS

Add the following:

■(208) ANTI-FACTOR Xa AND ANTI-FACTOR IIa ASSAYS FOR UNFRACTIONATED AND LOW MOLECULAR WEIGHT HEPARINS

This chapter provides information and procedures to determine factor Xa inhibitory activity and factor IIa (thrombin) inhibitory activity for unfractionated heparin (UFH) and low molecular weight heparins (LMWH).

INTRODUCTION

Unfractionated heparin and LMWH exert their anticoagulant effect by potentiating the activity of plasma coagulation inhibitors. Of all the commonly known glycosaminoglycans, only UFH, LMWH, and heparan sulfate (hereafter referred to generally as heparin) contain a specific pentasaccharide sequence that can bind to the plasma coagulation inhibitor, antithrombin (AT). AT-dependent assays, therefore, are developed to ensure the specificity of the methods for measuring the anticoagulant activity of heparin. Binding of heparin to AT induces a conformational change, thereby increasing AT's binding to and subsequent inactivation of activated blood coagulation factors. The major coagulation targets for the AT–heparin complex are factor IIa (thrombin) and coagulation factor Xa. Once AT is activated by the pentasaccharide sequence of heparin, it interacts with factors Xa and IIa

via its reactive center loop. For efficient inhibition of thrombin, the heparin molecule also must bind to both AT and IIa. This interaction requires an extra length of approximately 13 monosaccharides attached at the nonreducing end of the AT-binding heparin pentasaccharide sequence. This minimum heparin motif for AT inhibition of thrombin, known as the C-domain, has an approximate molecular weight of 5400 Da. Although the potentiation of AT inactivation of factor Xa also depends on molecular weight, the additional saccharide units of the C-domain are not essential, and heparin with a molecular weight less than 5400 Da can potentiate AT to inactivate factor Xa. By convention, the potency ratio of anti-factor Xa to anti-factor IIa for UFH is 1. Unfractionated heparin is heterogeneous and polydisperse but contains little or no material of molecular weight less than 5400 Da. The mean molecular weights of LMWH products are lower than those of UFH, and they contain a higher proportion of material that weighs less than 5400 Da. The potency ratio of anti-factor Xa to anti-factor IIa for LMWH products is greater than 1.5. This chapter describes assay procedures for the measurement of anti-factor Xa and anti-factor IIa activity of LMWH heparin in the presence of AT.

In the test system, heparin is bound to AT, and factor IIa or factor Xa added to the mixture binds to the heparin–AT complex. The residual factor IIa or factor Xa not inhibited by the heparin–AT complex is quantified by a chromogenic substrate that is specific for either factor IIa or factor Xa and is added in the final step. Analysts note an inverse relationship wherein more color is produced by more residual enzyme, which equates to less heparin activity.

As for any enzymatic assay, temperature and timing of the reaction, proper handling of the reagents, and the order in which the reagents are added are critical to the optimal performance of the assay.

ANTI-FACTOR Xa AND ANTI-FACTOR IIa ASSAYS FOR UNFRACTIONATED HEPARIN

Anti-Factor Xa Activity for UFH

The following procedure is used where specified in the individual monographs. This assay can be performed manually in plastic tubes utilizing heated block stations or water bath. Microtiter plate equipment with a reader and automated coagulometer can improve reproducibility and throughput.

pH 8.4 buffer: Dissolve amounts of tris(hydroxymethyl)aminomethane, edetic acid or edetate sodium, and sodium chloride in water containing 0.1% of polyethylene glycol 6000 to obtain solutions having concentrations of 0.050 M, 0.0075 M, and 0.175 M, respectively. Adjust, if necessary, with hydrochloric acid or sodium hydroxide solution to a pH of 8.4.

Antithrombin solution: Reconstitute a vial of antithrombin (see *Reagents, Indicators, and Solutions—Reagent Specifications*) as directed by the manufacturer, and further dilute with pH 8.4 buffer to obtain a solution having a concentration of 1.0 Antithrombin IU/mL.

Factor Xa solution: Reconstitute bovine factor Xa as directed by the manufacturer (see *Factor Xa in Reagents, Indicators, and Solutions—Reagent Specifications*), and further dilute in pH 8.4 buffer to obtain a solution that gives an absorbance value of 0.65–1.25 at 405 nm when assayed as described below but using 30 μ L of pH 8.4 buffer instead of 30 μ L of the *Standard solutions* or the *Sample solutions*. [NOTE—Factor Xa solution contains about 3 nanokatalytic units/mL but can vary depending on the manufacturer of factor Xa or the substrate used.]

Chromogenic substrate solution: Prepare a solution of a suitable chromogenic substrate for amidolytic test (see *Reagents, Indicators, and Solutions—Reagent Specifications*) spe-

cific for factor Xa in water to obtain a concentration of 1 mM.

Stopping solution: 20% (v/v) solution of acetic acid

Standard solutions: Reconstitute the entire contents of an ampule of USP Heparin Sodium for Assays RS with water, and dilute with *pH 8.4 buffer* to obtain at least 5 dilutions in the concentration range of 0.03–0.375 USP Heparin Units/mL.

Sample solutions: Dissolve or dilute an accurately measured quantity of Heparin Sodium in *pH 8.4 buffer*, and dilute with the same buffer to obtain solutions having activities approximately equal to those of the *Standard solutions*.

Analysis: [NOTE—The procedure also can be performed using alternative platforms. Perform the test with each *Standard solution* and *Sample solution* in duplicate.]

To each of a series of suitable plastic tubes placed in a water bath set at 37°, transfer 120 µL of *pH 8.4 buffer*. Then separately transfer 30 µL of the different dilutions of the *Standard solutions* or the *Sample solutions* to the tubes. Add 150 µL of *Antithrombin solution*, prewarmed at 37° for 15 min, to each tube, mix, and incubate for 2 min. Add 300 µL of *Factor Xa solution*, prewarmed at 37° for 15 min, to each tube, mix, and incubate for 2 min. Add 300 µL of *Chromogenic substrate solution*, prewarmed at 37° for 15 min, to each tube, mix, and incubate for exactly 2 min. Add 150 µL of *Stopping solution* to each tube, and mix. Prepare a blank for zeroing the spectrophotometer by adding the reagents in reverse order, starting with the *Stopping solution* and ending with the addition of 150 µL of *pH 8.4 buffer*, and excluding the *Standard solutions* or the *Sample solutions*. Record the absorbance at 405 nm against the blank. The volume of the reactants can be increased or decreased to suit the assay format provided that the proportions of the reference sample or the test sample and the reagents are kept the same.

Calculations: Plot the log of the absorbance values of the *Standard solutions* and the *Sample solutions* vs. heparin concentrations in USP Units. Calculate the activity of heparin sodium in USP Units/mg using statistical methods for slope ratio assays. Calculate the anti-factor Xa activity of heparin sodium:

$$A \times (S_T/S_S)$$

A = the potency of USP Heparin Sodium for Assays RS

S_T = slope of the line for the *Sample solutions*

S_S = slope of the line for the *Standard solutions*

Express the anti-factor Xa activity of the *Sample solution* as USP Heparin Units/mg, calculated on the dried basis. Calculate the ratio of anti-factor Xa activity against anti-factor IIa potency (see *Assay below*):

anti-factor Xa activity/anti-factor IIa potency

Acceptance criteria: 0.9–1.1

Anti-Factor IIa Activity for Unfractionated Heparin

pH 8.4 buffer: Dissolve 6.10 g of tris(hydroxymethyl)aminomethane, 10.20 g of sodium chloride, 2.80 g of edetate sodium, and, if suitable, 0–10.00 g of polyethylene glycol 6000 and/or 2.00 g of bovine serum albumin in 800 mL of water. [NOTE—2.00 g of human albumin may be substituted for 2.00 g of bovine serum albumin.] Adjust with hydrochloric acid to a pH of 8.4, and dilute with water to 1000 mL.

Antithrombin solution: Reconstitute a vial of antithrombin (see *Reagents, Indicators, and Solutions—Reagent Specifications*) in water to obtain a solution of 5 Antithrombin IU/mL. Dilute this solution with *pH 8.4 buffer* to obtain a

solution having a concentration of 0.125 Antithrombin IU/mL.

Thrombin human solution: Reconstitute thrombin human (factor IIa) (see *Reagents, Indicators, and Solutions—Reagent Specifications*) in water to obtain a solution of 20 Thrombin IU/mL, and dilute with *pH 8.4 buffer* to obtain a solution having a concentration of 5 Thrombin IU/mL.

[NOTE—The thrombin should have a specific activity of NLT 750 IU/mg.]

Chromogenic substrate solution: Prepare a solution of a suitable chromogenic thrombin substrate for amidolytic test (see *Reagents, Indicators, and Solutions—Reagent Specifications*) in water to obtain a concentration of 1.25 mM.

Stopping solution: 20% (v/v) solution of acetic acid

Standard solutions: Reconstitute the entire contents of an ampule of USP Heparin Sodium for Assays RS with water, and dilute with *pH 8.4 buffer* to obtain at least four dilutions in the concentration range of 0.005–0.03 USP Heparin Unit/mL.

Sample solutions: Proceed as directed for *Standard solutions* to obtain concentrations of Heparin Sodium similar to those obtained for the *Standard solutions*.

Analysis: [NOTE—The procedure also can be performed using alternative platforms.] For each dilution of the *Standard solutions* and the *Sample solutions*, at least duplicate samples should be tested. Label a suitable number of tubes depending on the number of replicates that will be tested. For example, if five blanks will be used: B1, B2, B3, B4, and B5 for the blanks; T1, T2, T3, and T4 each at least in duplicate for the dilutions of the *Sample solutions*; and S1, S2, S3, and S4 each at least in duplicate for the dilutions of the *Standard solutions*. Distribute the blanks over the series in such a way that they accurately represent the behavior of the reagents during the experiments. [NOTE—Treat the tubes in the order B1, S1, S2, S3, S4, B2, T1, T2, T3, T4, B3, T1, T2, T3, T4, B4, S1, S2, S3, S4, B5.] Note that after each addition of a reagent, the incubation mixture should be mixed without allowing bubbles to form. Add twice the volume (100–200 µL) of *Antithrombin solution* to each tube containing one volume (50–100 µL) of either the *pH 8.4 buffer* or an appropriate dilution of the *Sample solutions* or the *Standard solutions*. Mix, but do not allow bubbles to form. Incubate at 37° for at least 1 min. Add to each tube 25–50 µL of *Thrombin human solution*, and incubate for at least 1 min. Add 50–100 µL of *Chromogenic substrate solution*. Note that all reagents, *Standard solutions*, and *Sample solutions* should be prewarmed to 37° just before use. The volume of the reactants can be increased or decreased to suit the assay format provided that the proportions of the reference sample or the test sample and the reagents are kept the same.

Two different types of measurements can be recorded:

1. Endpoint Measurement: Stop the reaction after at least 1 min with 50–100 µL of *Stopping solution*. Measure the absorbance of each solution at 405 nm using a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* (851)). The RSD over the blank readings is less than 10%.
2. Kinetic Measurement: Follow the change in absorbance for each solution over 1 min at 405 nm using a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* (851)). Calculate the change in absorbance/min ($\Delta OD/min$). The blanks for kinetic measurement are also expressed as $\Delta OD/min$ and should give the highest values because they are carried out in the absence of heparin. The RSD over the blank readings is less than 10%.

Calculations: The statistical models for *Slope ratio assay* or *Parallel-line assay* can be used depending on which model best describes the correlation between concentration and response.

Slope ratio assay: For each series, calculate the regression of the log absorbance or the log change in absorb-

ance/min against concentrations of the *Sample solutions* and of the *Standard solutions*, and calculate the potency of heparin sodium in USP Units/mL using statistical methods for slope ratio assays. Express the potency of heparin sodium/mg, calculated on the dried basis.

Parallel-line assay: For each series, calculate the regression of the absorbance or change in absorbance/min against log concentrations of the *Sample solutions* and the *Standard solutions*, and calculate the potency of heparin sodium in USP Units/mL using statistical methods for parallel-line assays. Express the potency of heparin sodium/mg, calculated on the dried basis.

Acceptance criteria: The potency of heparin sodium, calculated on the dried basis, is NLT 180 USP Heparin Units in each mg.

USP Reference Standards (11): USP Heparin Sodium for Assays RS

ANTI-FACTOR Xa AND ANTI-FACTOR IIa ASSAYS FOR LOW MOLECULAR WEIGHT HEPARINS

The following procedure is used where specified in the individual monographs. This assay can be performed manually in plastic tubes utilizing heated block stations or water bath. Microtiter plate equipment with a reader and automated coagulometer can improve reproducibility and throughput. Acetic acid solution (stopping solution) is used for manual and microtiter plate assay. Automated coagulometers measure initial kinetic rate, and because of that, stopping of the reaction is not needed.

Anti-Factor Xa Activity for Low Molecular Weight Heparin

Acetic acid solution: Glacial acetic acid and water (42:58)

pH 7.4 polyethylene glycol 6000 buffer: Dissolve 6.08 g of tris(hydroxymethyl)aminomethane and 8.77 g of sodium chloride in 500 mL of water. Add 1.0 g of polyethylene glycol 6000 or 10.0 g of bovine serum albumin, adjust with hydrochloric acid to pH 7.4, and dilute with water to 1000 mL.

pH 7.4 buffer: Dissolve 6.08 g of tris(hydroxymethyl)aminomethane and 8.77 g of sodium chloride in 500 mL of water. Adjust with hydrochloric acid to pH 7.4, and dilute with water to 1000 mL.

pH 8.4 buffer: Dissolve 3.03 g of tris(hydroxymethyl)aminomethane, 5.12 g of sodium chloride, and 1.40 g of edetate sodium in 250 mL of water. Adjust with hydrochloric acid to a pH of 8.4, and dilute with water to 500 mL.

Human antithrombin solution: Reconstitute a vial of human antithrombin (see *Reagents, Indicators, and Solutions—Reagent Specifications*) in water to obtain a solution containing 5 Antithrombin Units per mL. Dilute this solution with pH 7.4 polyethylene glycol 6000 buffer to obtain a solution having a concentration of 1.0 Antithrombin Unit/mL.

Factor Xa solution: Reconstitute an accurately weighed quantity of bovine factor Xa (see *Reagents, Indicators, and Solutions—Reagent Specifications*) as directed by the manufacturer's instructions. Further dilute the stock solution with pH 7.4 polyethylene glycol 6000 buffer to obtain a solution that gives an increase in absorbance value at 405 nm of NMT 0.20 absorbance units/min or 0.8 absorbance units after 4 min of incubation with the chromogenic substrate when assayed as described below but using as an appropriate volume, *V*, the volume in μL of pH 7.4 buffer instead of *V* μL of the standard or the sample solution.

Chromogenic substrate solution: Prepare a solution of a suitable chromogenic substrate for amidolytic test (see *Reagents, Indicators, and Solutions—Reagent Specifications*) for factor Xa in water to obtain a concentration of about 3 mM. Dilute with substrate pH 8.4 buffer to obtain a solution having a concentration of 0.5 mM. [NOTE—Preheat reagents to $37 \pm 1^\circ$ 15 min before use.]

Standard solutions: Reconstitute and dilute the entire contents of an ampule of USP Low Molecular Weight Heparin for Bioassays RS with distilled water and then further dilute with pH 7.4 buffer to obtain at least four dilutions in the concentration range of 0.025–0.2 USP anti-factor Xa Units/mL.

Sample solutions: Proceed as directed for *Standard solutions* to obtain concentrations of LMWH similar to those obtained for the *Standard solutions*.

Analysis

Samples: *Standard solutions, Sample solutions, Human antithrombin solution, pH 7.4 buffer, Factor Xa solution, Chromogenic substrate solution, and Acetic acid solution*

Label 18 suitable tubes: B1 and B2 for blanks; T1, T2, T3, and T4 each in duplicate for the dilutions of the *Sample solutions*; and S1, S2, S3, and S4 each in duplicate for the dilutions of the *Standard solutions*. [NOTE—Treat the tubes in the order B1, S1, S2, S3, S4, T1, T2, T3, T4, T1, T2, T3, T4, S1, S2, S3, S4, B2.] To each tube add 50 μL of *Human antithrombin solution* and an equal volume, *V*, of either the blank, pH 7.4 buffer, or an appropriate dilution of the *Sample solutions* or the *Standard solutions*. Mix, but do not allow bubbles to form. Incubate at 37° for 1.0 min. Add to each tube 100 μL of *Factor Xa solution*, and incubate for 1.0 min. Add 250 μL of *Chromogenic substrate solution*. Stop the reaction after about 4.0 min with 250 μL of *Acetic acid solution*. Measure the absorbance of each solution at 405 nm using a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* (851)). Use quartz or disposable polystyrene cuvettes. The volume of the reactants can be increased or decreased to suit the assay format provided that the proportions of the reference sample or the test sample and the reagents are kept the same.

System suitability: The assay is valid if the following requirements are met:

1. A blank solution gives an increase in absorbance value at 405 nm of NMT 0.20 absorbance units/min (or 0.8 absorbance units in total) when assayed using an appropriate volume (50 μL) of pH 7.4 buffer instead of 50 μL of the *Standard solution* or the *Sample solution*.
2. The reading of the blank B2 is not more than ± 0.05 absorbance units against blank B1.

Calculations: For this bioassay, parallel-line or slope ratio analysis can be applied.

Calculate the potency of the test sample in USP anti-factor Xa Unit/mL, using a statistical model for parallel assays, plotting absorbance against log concentrations of the *Sample solutions* and of the *Standard solutions*. In some cases, log transformation of absorbance may be needed to obtain linearity for the dose-response curves. The assay is valid when the data fulfill the acceptance criteria for regression, linearity, and parallelism as required for parallel line assay. For slope ratio analysis, plot absorbance against concentrations of *Sample solutions* and of the *Standard solutions*. In some cases, log transformation of absorbance may be needed to obtain linearity for the dose-response curves. The assay is valid when the data fulfill the acceptance criteria for regression, linearity, and common intercept as required for slope ratio assay (see *Design and Analysis of Biological Assays* (111) and *Analysis of Biological Assays* (1034)).

Express the anti-factor Xa activity of sample/mg, calculated on the dried basis:

$$\text{Anti-factor Xa USP Unit/mg} = [\text{standard potency (USP Unit/mL)} \times \text{potency ratio}] / [\text{sample concentration (mg/mL)}]$$

Anti-Factor IIa Activity for Low Molecular Weight Heparin

Acetic acid solution, pH 7.4 polyethylene glycol 6000 buffer, pH 7.4 buffer, pH 8.4 buffer, and Human antithrombin solution: Proceed as directed in the *Anti-Factor Xa Activity*, except that the concentration of the *Human antithrombin solution* is 0.5 Antithrombin Unit/mL.

Thrombin human solution: Reconstitute thrombin (see *Reagents, Indicators, and Solutions—Reagent Specifications*) in water, and dilute in *pH 7.4 polyethylene glycol 6000 buffer* to obtain a solution having a concentration of 5 Thrombin Units/mL. Use the *Thrombin human solution* immediately after preparation.

Chromogenic substrate solution: Prepare a solution of a suitable chromogenic substrate for the amidolytic test (see *Reagents, Indicators, and Solutions—Reagent Specifications*) for thrombin in water to obtain a concentration of about 3 mM. Dilute immediately before use with *pH 8.4 buffer* to 0.5 mM.

Standard solutions: Reconstitute and dilute the entire contents of an ampule of USP Low Molecular Weight Heparin for Bioassays RS with distilled water, and further dilute with *pH 7.4 buffer* to obtain at least four dilutions having concentrations in the range of 0.015–0.075 USP Unit of anti-factor IIa activity/mL.

Sample solutions: Proceed as directed for *Standard solutions* to obtain concentrations of LMWH similar to those obtained for the *Standard solutions*.

Procedure: Proceed as directed under *Anti-Factor Xa Activity*, but use *Thrombin human solution* instead of *Factor Xa solution* and use the *Human antithrombin solution* as described above.

System suitability: The assay is valid if the following requirement is met:

1. The reading of blank B2 is NMT ± 0.05 absorbance units against blank B1.

Calculations: Proceed as directed for calculation of *Anti-Factor Xa Activity*.

USP Reference Standards (11): USP Low Molecular Weight Heparin for Bioassays RS_{1S} (USP36)

Where the limits to be applied comply with those given below, tests for residual solvents are not generally mentioned in specific monographs, because the solvents employed may vary from one manufacturer to another.

The objective of this general chapter is to provide acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. The chapter recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This general chapter does not address solvents deliberately used as excipients, nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Solvents that are known to cause unacceptable toxicities (Class 1, *Table 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Solvents associated with less severe toxicity (Class 2, *Table 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, *Table 3*) should be used where practical. The complete list of solvents included in this general chapter is given in *Appendix 1*. These tables and the list are not exhaustive. For the purposes of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for the use of a new solvent not currently listed in this general chapter, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent, the approved residual solvent limit in the article, and the appropriate test procedure for this residual solvent in the article. The USP will then address this topic in the individual monograph. When a new solvent has been approved through the ICH process, it will be added to the appropriate list in this general chapter. At that time, consideration will be given for removal of the specific solvent test requirement in the individual monograph.

Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification of drug substances, excipients, or products.

Although manufacturers may choose to test the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that provided in this general chapter, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. A drug product should also be tested if a residual solvent is used during its manufacture.

For the purposes of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for a higher level of residual solvent, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent and the approved residual solvent

OTHER TESTS AND ASSAYS

<467> RESIDUAL SOLVENTS

INTRODUCTION

This general chapter applies to existing drug substances, excipients, and products. All substances and products are subject to relevant control of solvents likely to be present in a substance or product.

limit in the article. The USP will then address this topic in the individual monograph.

See *Appendix 2* for additional background information related to residual solvents.

CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

The term *tolerable daily intake* (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals, and the term *acceptable daily intake* (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The term *permitted daily exposure* (PDE) is defined as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents assessed in this general chapter are listed in *Appendix 1* by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Residual Solvent Class	Assessment
Class 1	Solvents to be avoided Known human carcinogens Strongly suspected human carcinogens Environmental hazards
Class 2	Solvents to be limited Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity Solvents suspected of other significant but reversible toxicities
Class 3	Solvents with low toxic potential Solvents with low toxic potential to humans; no health-based exposure limit is needed [NOTE—Class 3 residual solvents have PDEs of 50 mg or more per day.*]

* For residual solvents with PDEs of more than 50 mg per day, see the discussion in the section *Class 3* under *Limits of Residual Solvents*.

METHODS FOR ESTABLISHING EXPOSURE LIMITS

The method used to establish PDEs for residual solvents is presented in *Appendix 3*.

For articles that are designated “for veterinary use only”, higher levels for the PDE and concentration limit may be justified in exceptional cases based upon the actual daily dose, actual target species, and relevant toxicological data and considering consumer safety impact. For the purpose of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for a higher limit, it is the responsibility of that manufacturer to notify the USP regarding the approved residual solvent limit in the article and the justification. The USP will then address this topic in the individual monograph.

OPTIONS FOR DESCRIBING LIMITS OF CLASS 2 RESIDUAL SOLVENTS

Two options are available when setting limits for Class 2 residual solvents.

Option 1

The concentration limits in ppm stated in *Table 2* are used. They were calculated using the equation below by assuming a product weight of 10 g administered daily.

$$\text{Concentration (ppm)} = (1000 \mu\text{g/mg} \times \text{PDE})/\text{dose}$$

Here, PDE is given in terms of mg per day, and dose is given in g per day.

These limits are considered acceptable for all drug substances, excipients, and drug products. Therefore, this option may be applied if the daily dose is not known or fixed. If all drug substances and excipients in a formulation meet the limits given in *Option 1*, these components may be used in any proportion. No further calculation is necessary, provided that the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day are to be considered under *Option 2*.

Option 2

It is not necessary for each component of the drug product to comply with the limits given in *Option 1*. The PDE in terms of mg per day as stated in *Table 2* can be used with the known maximum daily dose and the equation above to determine the concentration of residual solvent allowed in a drug product. Such limits are considered acceptable, provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. The limits should also reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the application of *Option 1* and *Option 2* to acetonitrile concentration in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus, the *Option 1* limit is 410 ppm. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	5.0	728	3.64

Excipient 1 meets the *Option 1* limit, but the drug substance, excipient 2, and drug product do not meet the *Option 1* limit. Nevertheless, the drug product meets the *Option 2* limit of 4.1 mg per day and thus conforms to the acceptance criteria in this general chapter.

Consider another example, using acetonitrile as the residual solvent. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	5.0	1016	5.08

In this example, the drug product meets neither the *Option 1* nor the *Option 2* limit according to this summation. The manufacturer could test the drug product to determine whether the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced to the allowed limit during formulation, the product fails to meet the solvent limits as described in this chapter, and the manufacturer of the drug product should take other steps to reduce the amount of acetonitrile in the drug product. In some instances, the manufacturer may have received approval from a competent regulatory authority for such a higher level of residual solvent. If this is the case, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent and the approved residual solvent limit in the article. The USP will then address this topic in the individual monograph.

ANALYTICAL PROCEDURES

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Compendial methods for testing for residual solvent content are described under the section *Identification, Control, and Quantification of Residual Solvents* in this general chapter. The *General Notices* discuss the use of other methods in special circumstances (see 6.30. *Alternative and Harmonized Methods and Procedures*). If Class 3 solvents are present, a nonspecific method such as loss on drying may be used.

REPORTING LEVELS OF RESIDUAL SOLVENTS

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in drug substances or excipients in order to meet the criteria of this general chapter. The following statements are given as acceptable examples of the information that could be provided from a supplier of drug substances or excipients to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5%.
- Only Class 2 solvents X, Y, ... are likely to be present. All are below the *Option 1* limit. (Here the supplier would name the Class 2 solvents represented by X, Y, ...)
- Only Class 2 solvents X, Y, ... and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the *Option 1* limit, and residual Class 3 solvents are below 0.5%.

The phrase “likely to be present”, as used in the above examples, refers to the solvent used or produced in the final manufacturing step and to solvents that are used or produced in earlier manufacturing steps and not removed consistently by a validated process.

If Class 1 solvents are likely to be present, they should be identified and quantified. If solvents of Class 2 or 3 are present at greater than their *Option 1* limits or 0.5%, respectively, they should be identified and quantified.

Change to read:

LIMITS OF RESIDUAL SOLVENTS

Class 1 (solvents to be avoided)

Class 1 residual solvents (*Table 1*) should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if their use in order to produce a medicinal product with a significant therapeutic advance is unavoidable, their levels should be restricted as shown in *Table 1*, unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in *Table 1* because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of safety data.

When Class 1 residual solvents are used or produced in the manufacture or purification of a drug substance, excipient, or drug product and are not removed by the process, these solvents should be identified and quantified. The procedures described in the section *Identification, Control, and Quantification of Residual Solvents* in this general chapter are to be applied wherever possible. Otherwise, an appropriate validated procedure is to be employed.

Table 1. Class 1 Residual Solvents
(Solvents that should be avoided)

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2

Class 2 residual solvents (*Table 2*) should be limited in drug substances, excipients, and drug products because of the inherent toxicities of the residual solvents. PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of the determination procedure. Precision should be determined as part of the procedure validation.

If Class 2 residual solvents are present at greater than their *Option 1* limits, they should be identified and quantified. The procedures described in the section *Identification, Control, and Quantification of Residual Solvents* in this general chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. [NOTE—The following Class 2 residual solvents are not readily detected by the headspace injection conditions described in the section *Identification, Control, and Quantification of Residual Solvents* in this general chapter: formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, *N*-methylpyrrolidone, and sulfolane. Other appropriate validated procedures are to be employed for the quantification of these residual solvents. Such procedures shall be submitted to the USP for review and possible inclusion in the relevant individual monograph. In addition, USP Residual Solvent Class 2—Mixture C RS can be used to develop an alternative procedure.]

Table 2. Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
■Cumene	0.7	70■1S (USP36)
Cyclohexane	38.8	3880
1,2-Dichloroethane	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
Trichloroethylene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

Class 3

Class 3 residual solvents (*Table 3*) may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5% under *Option 1*) would be acceptable without justification. Higher amounts may also be acceptable, provided that they are realistic in relation to manufacturing capability and good manufacturing practice. For the purposes of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for such a higher level of residual solvent, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent and the approved residual solvent limit in the article. The USP will then address this topic in the individual monograph. If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified. The procedures described in the section *Identification, Control, and Quantification of Residual Solvents* in this general chapter, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise, an appropriate validated procedure is to be employed.

Table 3. Class 3 Residual Solvents

(Limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
<i>tert</i> -Butylmethyl ether	Methylisobutylketone
■1S (USP36)	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Other Residual Solvents

The residual solvents listed in *Table 4* may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on which to base a PDE was found.

Table 4. Other Residual Solvents

(For which no adequate toxicological data was found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

Whenever possible, the substance under test needs to be dissolved to release the residual solvent. Because the USP deals with drug products, as well as active ingredients and excipients, it may be acceptable that in some cases, some of the components of the formulation will not dissolve completely. In those cases, the drug product may first need to be pulverized into a fine powder so that any residual solvent that may be present can be released. This operation should be performed as fast as possible to prevent the loss of volatile solvents during the procedure.

[NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.]

Class 1 and Class 2 Residual Solvents

The following procedures are useful to identify and quantify residual solvents when the information regarding which solvents are likely to be present in the material is not available. When the information about the presence of specific residual solvents is available, only *Procedure C* is needed to quantify the amount of residual solvents present. A flow diagram for the application of the residual solvent limit tests is shown in *Figure 1*.

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—[NOTE—When transferring solutions, place the tip of the pipet just below the sur-

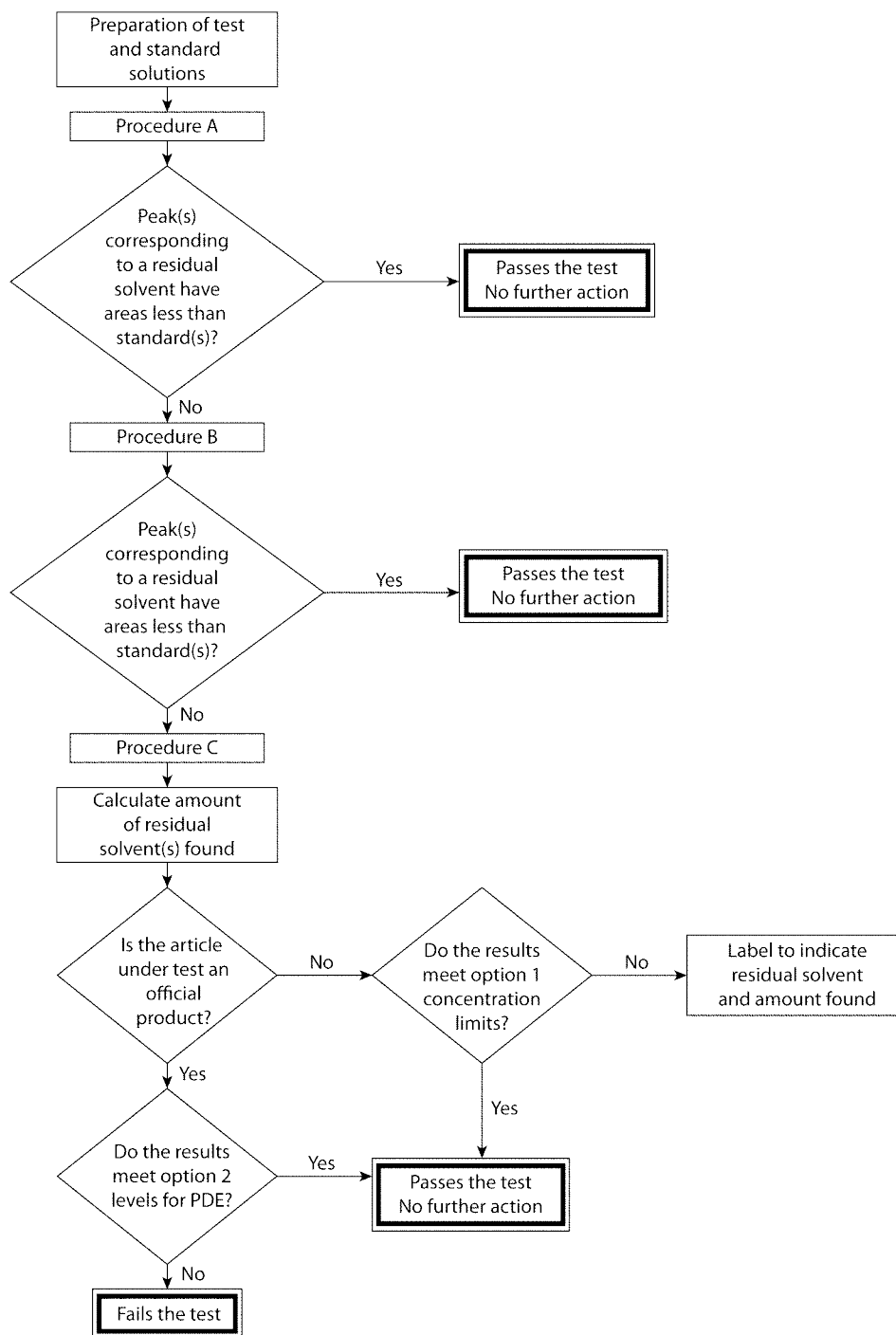


Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.

face of the liquid, and mix.] Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, previously filled with about 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, previously filled with about 50 mL of water, dilute with water to volume, and mix. Transfer 10 mL of this solution to a 100-mL volumetric flask, previously filled with about 50 mL of water, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial containing 5.0 mL of water (place the tip of the pipet just

below the surface of the liquid for dispensing), apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A*. Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B*.

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate head-

space vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution*, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* (621))—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m fused-silica column coated with a 1.8-μm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm/s, and a split ratio of 1:5. [NOTE—The split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 min, then raised at a rate of 10° per min to 240°, and maintained at 240° for 20 min. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, *Class 1 System Suitability Solution*, and *Class 2 Mixture A Standard Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is NLT 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is NLT 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is NLT 1.0.

Procedure—[NOTE—It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.] Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, and *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in the *Class 1 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 2 Standard Stock Solutions*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, *Test Stock Solution*, *Test Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A*.

Chromatographic System (see *Chromatography* (621))—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m fused-silica column coated with a 0.25-μm layer of phase G16 or a 0.53-mm × 30-m wide-bore column coated with a 0.25-μm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm/s and a split ratio of 1:5. [NOTE—The split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 50° for 20 min, then raised at a rate of 6° per min to 165°, and maintained at 165° for 20 min. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution* and the *Class 1 System Suitability Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is NLT 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is NLT 3; and the resolution, *R*, between acetonitrile and *cis*-dichloroethene in the *Class 2 Mixture A Standard Solution* is NLT 1.0.

Procedure—[NOTE—It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.] Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 2 Standard Stock Solution A*, *Class 2 Mixture A Standard Solution*, *Test Stock Solution*, *Test Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A*.

Standard Stock Solution—[NOTE—Prepare a separate *Standard Stock Solution* for each peak identified and verified by *Procedures A* and *B*. For the *Class 1* solvents other than 1,1,1-trichloroethane, prepare the first dilution as directed for the first dilution under *Class 1 Standard Stock Solution* in *Procedure A*.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a so-

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min)	60	45	45
Transfer-line temperature (°) (if appropriate)	85	110	105
Syringe temperature (°) (if appropriate)	80–90	105–115	80–90
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time(s) (if appropriate)	≥60	≥60	≥60
Injection volume (mL)*	1	1	1

* Or follow the instrument manufacturer's recommendations, as long as the method criteria are met. Injecting less than this amount is allowed as long as adequate sensitivity is achieved.

lution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*).

Standard Solution—Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B*.] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Stock Solution*, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* <621>)—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B*, the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m fused-silica column coated with a 1.8-μm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm/s, and a split ratio of 1:5. [NOTE—The split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 min, then raised at a rate of 10° per min to 240°, and maintained at 240° for 20 min. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, the *Class 1 System Suitability Solution*, and the *Class 2 Mixture A Standard Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is NLT 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is NLT 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is NLT 1.0.

Procedure—[NOTE—It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.] Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution*, *Test Solution*, and the *Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which *C* is the concentration, in μg per mL, of the appropriate USP Reference Standard in the *Standard Stock Solution*; *W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution*; and *r_U* and *r_{ST}* are the peak responses of each residual solvent obtained from the *Test Solution* and the *Spiked Test Solution*, respectively.

WATER-INSOLUBLE ARTICLES

Procedure A—[NOTE—Dimethyl sulfoxide may be substituted as an alternative solvent to dimethylformamide.]

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix (reserve a portion of this solution for the *Class 1 System Suitability Solution*). Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. This is *Class 2 Standard Stock Solution A*. Transfer 0.5 mL of USP Residual Solvents Class 2—Mixture B RS to a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix. This is *Class 2 Standard Stock Solution B*.

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial containing 5.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 500 mg of the article under test, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution—Transfer 1.0 mL of *Test Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Mix 5 mL of *Test Stock Solution* with 0.5 mL of the intermediate dilution reserved from *Class 1 Standard Stock Solution*. Transfer 1.0 mL of this solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* <621>)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm/s and a split ratio of 1:3. [NOTE—The split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 min, then raised at a rate of 10° per min to 240°, and maintained at 240° for 20 min. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, *Class 1 System Suitability Solution*, and *Class 2 Mixture A Standard Solution*, and record the peak responses as directed for *Procedure*: the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is NLT 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is NLT 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is NLT 1.0.

Procedure—[NOTE—It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.] Separately inject (use headspace operating parameters in column 3 of *Table 5* with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Mixture A Standard Solution*, *Class 2 Mixture B Standard Solution*, and *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in the *Class 1 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise, the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, and Class 2 Mixture B Standard Solution, Test Stock Solution, and Test Solution—Proceed as directed for *Procedure A*.

Chromatographic System—Proceed as directed for *Procedure B* under *Water-Soluble Articles* with a split ratio of 1:3. [NOTE—The split ratio can be modified in order to optimize sensitivity.]

Procedure—[NOTE—It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.] Separately inject (use headspace operating parameters in column 3 of *Table 5* with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, and Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or any of the two *Class 2 Mixture Standard Solutions*, proceed to *Procedure C* to quantify the peak(s); otherwise, the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, and Class 2 Mixture A Standard Solution—Proceed as directed for *Procedure A*.

Standard Stock Solution—[NOTE—Prepare a separate *Standard Stock Solution* for each peak identified and verified by *Procedures A* and *B*. For the *Class 1* solvents other than 1,1,1-trichloroethane, prepare the first dilution as directed for the first dilution under *Class 1 Standard Stock Solution* in *Procedure A*.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*).

Standard Solution—Transfer 1.0 mL of the *Standard Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Proceed as directed for *Procedure A*.

Test Solution—Transfer 1.0 mL of the *Test Stock Solution* to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B*.] Transfer 1.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1 mL of *Standard Stock Solution* and 4.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System—Proceed as directed for *Procedure C* under *Water-Soluble Articles*.

Procedure—[NOTE—It is recommended to increase the temperature of the transfer line between runs to eliminate any potential condensation of solvents.] Separately inject (use headspace operating parameters in column 3 of *Table 5* with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the *Standard Solution, Test Solution, and Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$10 \times (C/W)[r_U/(r_{ST} - r_U)]$$

in which *C* is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard Stock Solu-*

tion; *W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution*; and *r_U* and *r_{ST}* are the peak responses of each residual solvent obtained from *Test Solution* and *Spiked Test Solution*, respectively.

Class 3 Residual Solvents

If *Class 3* solvents are present, the level of residual solvents may be determined as directed under *Loss on Drying* (731) when the monograph for the article under test contains a loss on drying procedure specifying an upper limit of no more than 0.5% (per *Option 1* in this general chapter), or a specific determination of the solvent may be made. If there is no loss on drying procedure in the monograph for the article under test or if a *Class 3* solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*), the individual *Class 3* residual solvent or solvents present in the article under test should be identified and quantified, and the procedures as described above, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise, an appropriate validated procedure is to be employed. USP Reference Standards, where available, should be used in these procedures.

GLOSSARY

Acceptable daily intake (ADI): The maximum acceptable intake of toxic chemicals per day. This term is used by the World Health Organization (WHO).

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

Lowest-observed-effect level (LOEL): The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data so that the data can be safely related to humans.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.

No-observed-effect level (NOEL): The highest dose of a substance at which there are no biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Permitted daily exposure (PDE): The maximum acceptable intake per day of a residual solvent in pharmaceutical products.

Reversible toxicity: The occurrence of harmful effects that are caused by a substance and that disappear after exposure to the substance ends.

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but for which there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.




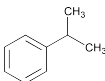


Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

Tolerable daily intake (TDI): Tolerable daily exposure to toxic chemicals. Term used by the International Program on Chemical Safety (IPCS).

Change to read:**APPENDIX 1. LIST**








See the table *Appendix 1. List of Residual Solvents Included in This General Chapter*.

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	<i>n</i> -Butyl alcohol Butan-1-ol	$\text{CH}_3(\text{CH}_2)_3\text{OH}$	Class 3
2-Butanol	<i>sec</i> -Butyl alcohol Butan-2-ol	$\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$\text{CH}_3\text{COO}(\text{CH}_2)_3\text{CH}_3$	Class 3
<i>tert</i> -Butylmethyl ether	2-Methoxy-2-methylpropane	$(\text{CH}_3)_3\text{COCH}_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	CHCl_3	Class 2
Cumene	Isopropylbenzene (1-Methylethyl)benzene		Class 2 <small>■ Class 2 ■ 115 (USP36)</small>
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	<i>sym</i> -Dichloroethane Ethylene dichloride Ethylene chloride	$\text{CH}_2\text{ClCH}_2\text{Cl}$	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$\text{H}_2\text{C}=\text{CCl}_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$\text{ClHC}=\text{CHCl}$	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl cellosolve	$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_3$	Class 2
<i>N,N</i> -Dimethylacetamide	DMA	$\text{CH}_3\text{CON}(\text{CH}_3)_2$	Class 2
<i>N,N</i> -Dimethylformamide	DMF	$\text{HCON}(\text{CH}_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(\text{CH}_3)_2\text{SO}$	Class 3
1,4-Dioxane	<i>p</i> -Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	$\text{CH}_3\text{CH}_2\text{OH}$	Class 3
2-Ethoxyethanol	Cellosolve	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$\text{CH}_3\text{COOCH}_2\text{CH}_3$	Class 3
Ethylene glycol	1,2-Dihydroxyethane 1,2-Ethanediol	$\text{HOCH}_2\text{CH}_2\text{OH}$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$\text{HCOOCH}_2\text{CH}_3$	Class 3
Formamide	Methanamide	HCONH_2	Class 2


* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER (Continued)

Solvent	Other Names	Structure	Class
Formic acid		HCOOH	Class 3
Heptane	<i>n</i> -Heptane	CH ₃ (CH ₂) ₅ CH ₃	Class 3
Hexane	<i>n</i> -Hexane	CH ₃ (CH ₂) ₄ CH ₃	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	CH ₃ COOCH ₂ CH(CH ₃) ₂	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	CH ₃ COOCH(CH ₃) ₂	Class 3
Methanol	Methyl alcohol	CH ₃ OH	Class 2
2-Methoxyethanol	Methyl cellosolve	CH ₃ OCH ₂ CH ₂ OH	Class 2
Methyl acetate	Acetic acid methyl ester	CH ₃ COOCH ₃	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	(CH ₃) ₂ CHCH ₂ CH ₂ OH	Class 3
Methylbutylketone	2-Hexanone Hexan-2-one	CH ₃ (CH ₂) ₃ COCH ₃	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylene chloride	Dichloromethane	CH ₂ Cl ₂	Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	CH ₃ CH ₂ COCH ₃	Class 3
Methyl isobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	CH ₃ COCH ₂ CH(CH ₃) ₂	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	(CH ₃) ₂ CHCH ₂ OH	Class 3
<i>N</i> -Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH ₃ NO ₂	Class 2
Pentane	<i>n</i> -Pentane	CH ₃ (CH ₂) ₃ CH ₃	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	CH ₃ (CH ₂) ₃ CH ₂ OH	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	CH ₃ CH ₂ CH ₂ OH	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	(CH ₃) ₂ CHOH	Class 3
Propyl acetate	Acetic acid propyl ester	CH ₃ COOCH ₂ CH ₂ CH ₃	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide		Class 2
Tetralin	1,2,3,4-Tetrahydronaphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH ₃ CCl ₃	Class 1

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER (Continued)

Solvent	Other Names	Structure	Class
Trichloroethylene	1,1,2-Trichloroethene	HCIC=CCl_2	Class 2
Xylene*	Dimethylbenzene Xylol		Class 2

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

APPENDIX 2. ADDITIONAL BACKGROUND

A2.1. Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in *Environmental Health Criteria* (EHC) monographs and in the Integrated Risk Information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (EPA), and the United States Food and Drug Administration (FDA) include the determination of acceptable exposure levels. The goal is maintenance of environmental integrity and protection of human health against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The procedures involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter-term study data can be used with modification of the approach, such as use of larger safety factors. The approach described therein relates primarily to long-term or lifetime exposure of the general population in the ambient environment (i.e., ambient air, food, drinking water, and other media).

A2.2. Residual Solvents in Pharmaceuticals

Exposure limits in this general chapter are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, the following specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits.

1. Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
2. The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
3. Residual solvents are unavoidable components in pharmaceutical production and will often be a part of medicinal products.
4. Residual solvents should not exceed recommended levels except in exceptional circumstances.
5. Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by the Organization for Economic Cooperation and Development (OECD), EPA, and the FDA *Red Book*.

APPENDIX 3. PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W., and Kodell, R.L. Linear Interpolation Algorithm for Low

Dose Assessment of Toxic Substance. *Journal of Environmental Pathology and Toxicology*, 4:305, 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 residual solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the no-observed-effect level (NOEL). Detection and quantification of these residual solvents should be performed by state-of-the-art analytical techniques.

Acceptable exposure levels in this general chapter for Class 2 residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (page 5748 of *PF 15*(6) [Nov.–Dec. 1989]), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (*Environmental Health Criteria 170*, WHO, 1994). These procedures are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA (*Red Book*) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values presented in *Table 2* of this document.

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL), in the most relevant animal study as follows:

$$\text{PDE} = (\text{NOEL} \times \text{Weight Adjustment}) / (F_1 \times F_2 \times F_3 \times F_4 \times F_5) \quad (1)$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of “uncertainty factors” used in *Environmental Health Criteria* (*Environmental Health Criteria 170*, WHO, Geneva, 1994) and “modifying factors” or “safety factors” in *Pharmacopoeial Forum*. The assumption of 100 percent systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 =	A factor to account for extrapolation between species
F1 =	2 for extrapolation from dogs to humans
F1 =	2.5 for extrapolation from rabbits to humans
F1 =	3 for extrapolation from monkeys to humans
F1 =	5 for extrapolation from rats to humans
F1 =	10 for extrapolation from other animals to humans
F1 =	12 for extrapolation from mice to humans

F1 takes into account the comparative surface area to body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67} \quad (2)$$

in which *M* = body weight, and the constant *k* has been taken to be 10. The body weights used in the equation are those shown below in *Table A3.1*.

F2 =	A factor of 10 to account for variability between individuals. A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this general chapter.
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F3 =	A variable factor to account for toxicity studies of short-term exposure
F3 =	1 for studies that last at least one half-lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys)
F3 =	1 for reproductive studies in which the whole period of organogenesis is covered
F3 =	2 for a 6-month study in rodents, or a 3.5-year study in nonrodents
F3 =	5 for a 3-month study in rodents, or a 2-year study in nonrodents
F3 =	10 for studies of a shorter duration

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

F4 =	A factor that may be applied in cases of severe toxicity, e.g., nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity. In studies of reproductive toxicity, the following factors are used:
F4 =	1 for fetal toxicity associated with maternal toxicity
F4 =	5 for fetal toxicity without maternal toxicity
F4 =	5 for a teratogenic effect with maternal toxicity
F4 =	10 for a teratogenic effect without maternal toxicity

F5 =	A variable factor that may be applied if the no-effect level was not established
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When only a LOEL is available, a factor of up to 10 can be used, depending on the severity of the toxicity. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kilograms (kg). This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg kg⁻¹ day⁻¹. The PDE for acetonitrile in this study is calculated as follows:

$$\text{PDE} = (50.7 \text{ mg kg}^{-1} \text{ day}^{-1} \times 50 \text{ kg}) / (12 \times 10 \times 5 \times 1 \times 1) = 4.22 \text{ mg day}^{-1}$$

In this example,

F1 =	12 to account for the extrapolation from mice to humans
F2 =	10 to account for differences between individual humans
F3 =	5 because the duration of the study was only 13 weeks
F4 =	1 because no severe toxicity was encountered
F5 =	1 because the no-effect level was determined

A3.1. Values Used in the Calculations in This Document

Rat body weight	425 g
Pregnant rat body weight	330 g
Mouse body weight	28 g
Pregnant mouse body weight	30 g
Guinea-pig body weight	500 g
Rhesus monkey body weight	2.5 kg
Rabbit body weight (pregnant or not)	4 kg
Beagle dog body weight	11.5 kg
Rat respiratory volume	290 L/day
Mouse respiratory volume	43 L/day
Rabbit respiratory volume	1440 L/day
Guinea-pig respiratory volume	430 L/day
Human respiratory volume	28,800 L/day
Dog respiratory volume	9000 L/day
Monkey respiratory volume	1150 L/day
Mouse water consumption	5 mL/day
Rat water consumption	30 mL/day
Rat food consumption	30 g/day

The equation for an ideal gas, $PV = nRT$, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m³. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6} \text{ atm} \times 153.840 \text{ mg mol}^{-1}}{0.082 \text{ L atm K}^{-1} \text{ mol}^{-1} \times 298 \text{ K}} = \frac{46.15 \text{ mg}}{24.45 \text{ L}} = 1.89 \text{ mg/L}$$

The relationship 1000 L = 1 m³ is used to convert to mg/m³.

Physical Tests and Determinations

(643) TOTAL ORGANIC CARBON

Change to read:

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, from biofilm growing in the system, and from the packaging of sterile and nonsterile waters. ■¹⁵ (USP36) TOC can also be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system. A TOC measurement is not a replacement test for endotoxin or microbiological control. Although there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation.

A number of acceptable methods exist for analyzing TOC. This chapter does not endorse, limit, or prevent any tech-

nologies from being used, but this chapter provides guidance on how to qualify these analytical technologies for use as well as guidance on how to interpret instrument results for use as a limit test.

Apparatuses commonly used to determine TOC in water for pharmaceutical use have in common the objective of oxidizing the organic molecules in the water to produce carbon dioxide followed by the measurement of the amount of carbon dioxide produced. Then the amount of CO₂ produced is determined and used to calculate the organic carbon concentration in the water.

All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved CO₂ and bicarbonate, and the CO₂ generated from the oxidation of organic molecules in the sample. The discrimination may be accomplished either by determining the inorganic carbon and subtracting it from the total carbon (total carbon is the sum of organic carbon and inorganic carbon), or by purging inorganic carbon from the sample before oxidation. Although purging may entrain organic molecules, such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

Change to read:

■BULK WATER

The following sections apply to tests for bulk *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and the condensate of *Pure Steam*.^{■15 (USP36)}

Apparatus Requirements: This test method is performed either as an on-line test or as an off-line laboratory test using a calibrated instrument. The suitability of the apparatus must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.05 mg/L (0.05 ppm) or lower of carbon.

When testing water for quality control purposes, ensure that the instrument and its data are under appropriate control and that the sampling approaches and locations of both on-line and off-line measurements are representative of the quality of the water used. The nature of the water production, distribution, and use should be considered when selecting either on-line or off-line measurement.

USP Reference Standards (11): USP 1,4-Benzoquinone RS. USP Sucrose RS.

Reagent Water: Use water having a TOC level of not more than 0.10 mg/L. [NOTE—A conductivity requirement may be necessary in order to ensure method reliability.]

Container Preparation: Organic contamination of containers results in higher TOC values. Therefore, use labware and containers that have been scrupulously cleaned of organic residues. Any method that is effective in removing organic matter can be used (see *Cleaning Glass Apparatus* (1051)). Use *Reagent Water* for the final rinse.

Standard Solution: Unless otherwise directed in the individual monograph, dissolve in the *Reagent Water* an accurately weighed quantity of USP Sucrose RS to obtain a solution having a concentration of 1.19 mg/L of sucrose (0.50 mg/L of carbon).

System Suitability Solution: Dissolve in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 0.75 mg/L (0.50 mg/L of carbon).

Reagent Water Control: Use a suitable quantity of *Reagent Water* obtained at the same time as that used in the preparation of the *Standard Solution* and the *System Suitability Solution*.

Water Sample: Obtain an on-line or off-line sample that suitably reflects the quality of water used.

Other Control Solutions: Prepare appropriate reagent blank solutions or other specified solutions needed for establishing the apparatus baseline or for calibration adjustments following the manufacturer's instructions, and run the appropriate blanks to zero the instrument, if necessary.

System Suitability: Test the *Reagent Water Control* in the apparatus, and record the response, r_w . Repeat the test using the *Standard Solution*, and record the response, r_s . Calculate the corrected *Standard Solution* response, which is also the limit response, by subtracting the *Reagent Water Control* response from the response of the *Standard Solution*. The theoretical limit of 0.50 mg/L of carbon is equal to the corrected *Standard Solution* response, $r_s - r_w$. Test the *System Suitability Solution* in the apparatus, and record the response, r_{ss} . Calculate the corrected *System Suitability Solution* response by subtracting the *Reagent Water Control* response from the response of the *System Suitability Solution*, $r_{ss} - r_w$. Calculate the percent response efficiency for the *System Suitability Solution*:

$$\% \text{ response efficiency} = 100[(r_{ss} - r_w)/(r_s - r_w)]$$

where r_{ss} is the instrument response to the *System Suitability Solution*; r_w is the instrument response to the *Reagent Water Control*; and r_s is the instrument response to the *Standard Solution*. The system is suitable if the percent response efficiency is not less than 85% and not more than 115%.

Procedure: Perform the test on the *Water Sample*, and record the response, r_u . The *Water Sample* meets the requirements if r_u is not more than the limit response, $r_s - r_w$. This method can be performed using on-line or off-line instrumentation that meets the *Apparatus Requirements*.

Add the following:

■STERILE WATER

The following sections apply to tests for *Sterile Water for Injection*, *Sterile Purified Water*, *Sterile Water for Irrigation*, and *Sterile Water for Inhalation*.

Follow the requirements in *Bulk Water*, with the following exceptions.

Apparatus Requirements: In addition to the *Apparatus Requirements* in *Bulk Water*, the apparatus must have a manufacturer's specified limit of detection of 0.10 mg/L (0.10 ppm) or lower of carbon.

Reagent Water: Use water having a TOC level of not more than 0.50 mg/L. [NOTE—A conductivity requirement may be necessary in order to ensure method reliability.]

Standard Solution: Unless otherwise directed in the individual monograph, dissolve in the *Reagent Water* an accurately weighed quantity of USP Sucrose RS to obtain a solution having a concentration of 19.0 mg/L of sucrose (8.0 mg/L of carbon).

System Suitability Solution: Dissolve in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 12.0 mg/L (8.0 mg/L of carbon).

Water Sample: Obtain a sample that suitably reflects the quality of water used. Before opening, vigorously agitate the package to homogenize the water sample. Several packages may be required in order to collect sufficient water for analysis.

System Suitability: Test the *Reagent Water Control* in the apparatus, and record the response, r_w . Repeat the test using the *Standard Solution*, and record the response, r_s . Calculate the corrected *Standard Solution* response, which is also the limit response, by subtracting the *Reagent Water Control* response from the response of the *Standard Solution*. The theoretical limit of 8.0 mg/L of carbon is equal to the corrected *Standard Solution* response, $r_s - r_w$. Test the *System*

Suitability Solution in the apparatus, and record the response, r_{SS} . Calculate the corrected *System Suitability Solution* response by subtracting the *Reagent Water Control* response from the response of the *System Suitability Solution*, $r_{SS} - r_W$. Calculate the percent response efficiency for the *System Suitability Solution*:

$$\% \text{ response efficiency} = 100[(r_{SS} - r_W)/(r_S - r_W)]$$

where r_{SS} is the instrument response to the *System Suitability Solution*; r_W is the instrument response to the *Reagent Water Control*; and r_S is the instrument response to the *Standard Solution*. The system is suitable if the percent response efficiency is not less than 85% and not more than 115%.

Procedure: Perform the test on the *Water Sample*, and record the response, r_U . The *Water Sample* meets the requirements if r_U is not more than the limit response, $r_S - r_W$, determined in the *System Suitability* requirements in *Sterile Water*. ■ 1S (USP36)

(645) WATER CONDUCTIVITY

Electrical conductivity in water is a measure of the ion-facilitated electron flow through it. Water molecules dissociate into ions as a function of pH and temperature and result in a very predictable conductivity. Some gases, most notably carbon dioxide, readily dissolve in water and interact to form ions, which predictably affect conductivity as well as pH. For the purpose of this discussion, these ions and their resulting conductivity can be considered intrinsic to the water.

Water conductivity is also affected by the presence of extraneous ions. The extraneous ions used in modeling the conductivity specifications described below are the chloride and sodium ions. The conductivity of the ubiquitous chloride ion (at the theoretical endpoint concentration of 0.47 ppm when it was a required attribute test in *USP XXII* and earlier revisions) and the ammonium ion (at the limit of 0.3 ppm) represent a major portion of the allowed water impurity level. A balancing quantity of cations, such as sodium ions, is included in this allowed impurity level to maintain electroneutrality. Extraneous ions such as these may have significant impact on the water's chemical purity and suitability for use in pharmaceutical applications. The procedure in the section *Bulk Water* is specified for measuring the conductivity of waters such as *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and the condensate of *Pure Steam*. The procedure in the section *Sterile Water* is specified for measuring the conductivity of waters such as *Sterile Purified Water*, *Sterile Water for Injection*, *Sterile Water for Inhalation*, and *Sterile Water for Irrigation*.

Online conductivity testing provides real-time measurements and opportunities for real-time process control, decision, and intervention. Precaution should be taken while collecting water samples for off-line conductivity measurements. The sample may be affected by the sampling method, the sampling container, and environmental factors such as ambient carbon dioxide concentration and organic vapors.

INSTRUMENT SPECIFICATIONS AND OPERATING PARAMETERS

Water conductivity must be measured accurately using calibrated instrumentation. The conductivity cell constant, a factor that represents the geometrical properties of the con-

ductivity sensor, must be known within $\pm 2\%$. The cell constant can be verified directly by using a solution of known or traceable conductivity, or indirectly by comparing the instrument reading taken with the conductivity sensor in question to readings from a conductivity sensor of known or traceable cell constant.

Meter calibration is accomplished by replacing the conductivity sensor with NIST (or equivalent local national authority)-traceable precision resistors (accurate to $\pm 0.1\%$ of the stated value) or an equivalently accurate adjustable resistance device, such as a Wheatstone Bridge, to give a predicted instrument response. Each scale on the meter may require separate calibration prior to use. The frequency of recalibration is a function of instrument design, degree of use, etc. However, because some multiple-scale instruments have a single calibration adjustment, recalibration may be required between each use of a different scale. Excluding the conductivity sensor cell constant accuracy, the instrument accuracy must be $\pm 0.1 \mu\text{S}/\text{cm}$.

In order to increase the measurement accuracy on the conductivity ranges used, which can be large, and to ensure a complete equipment calibration, it is suggested that periodic verification of the entire equipment be performed. This could be done by comparing the conductivity/resistivity values displayed by the measuring equipment with those of an external calibrated conductivity-measuring device. The two nontemperature-compensated conductivity or resistivity values must be equivalent to within $\pm 20\%$ of each other, or at a difference that is acceptable on the basis of product water criticality and/or the water conductivity ranges in which the measurements are taken. The two conductivity sensors should be positioned close enough together to measure the same water sample in the same environmental conditions.

In addition to the verification method performed in nontemperature-compensated mode, a similar verification performed in temperature-compensated mode could be performed to ensure an appropriate accuracy of the equipment when such a mode is used for trending or other purposes.

Because temperature has a substantial impact on conductivity readings of specimens at high and low temperatures, many instruments automatically correct the actual reading to display the value that theoretically would be observed at the nominal temperature of 25° . This is typically done using a temperature sensor embedded in the conductivity sensor and an algorithm in the instrument's circuitry. This temperature compensation algorithm may not be accurate. Conductivity values used in this method are nontemperature-compensated measurements. Temperature measurement is required for the performance of the *Stage 1* test. It may be made using the temperature sensor embedded in the conductivity cell sensor. An external temperature sensor positioned near the conductivity sensor is also acceptable. Accuracy of the temperature measurement must be $\pm 2^\circ$.

The procedures below shall be performed using instrumentation that has been calibrated, has conductivity sensor cell constants that have been accurately determined, and has a temperature compensation function that has been disabled. For both online and offline measurements, the suitability of instrumentation for quality control testing is also dependent on the sampling location(s) in the water system. The selected sampling instrument location(s) must reflect the quality of the water used.

BULK WATER

The procedure and test limits in this section are intended for *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, the condensate of *Pure Steam*, and any other monographs which specify this section.

The combined conductivities of the intrinsic and extraneous ions vary as a function of pH and are the basis for the conductivity specifications described in the *Stage 3—pH and Conductivity Requirements* table and used when performing *Stage 3* of the test method. Two preliminary stages are in-

cluded in the test method. If the test conditions and conductivity limits are met at either of these preliminary stages, the water meets the requirements of this test. Proceeding to the third stage of the test in these circumstances is unnecessary. Only in the event of failure at the final test stage is the sample judged noncompliant with the requirements of the test.

Procedure

STAGE 1

- Stage 1 is intended for online measurement or may be performed offline in a suitable container.
1. Determine the temperature of the water and the conductivity of the water using a nontemperature-compensated conductivity reading.
 2. Using the *Stage 1—Temperature and Conductivity Requirements* table, find the temperature value that is not greater than the measured temperature, i.e., the next lower temperature. The corresponding conductivity value on this table is the limit. [NOTE—Do not interpolate.]
 3. If the measured conductivity is not greater than the table value, the water meets the requirements of the test for conductivity. If the conductivity is higher than the table value, proceed with Stage 2.

Stage 1—Temperature and Conductivity Requirements
(for nontemperature-compensated conductivity measurements only)

Temperature	Conductivity Requirement (μS/cm)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

STAGE 2

4. Transfer a sufficient amount of water (100 mL or more) to a suitable container, and stir the test specimen. Adjust the temperature, if necessary, and, while maintaining it at $25 \pm 1^\circ$, begin vigorously agitating the test specimen while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than a net of 0.1 μS/cm per 5 min, note the conductivity.
5. If the conductivity is not greater than 2.1 μS/cm, the water meets the requirements of the test for conductivity. If the conductivity is greater than 2.1 μS/cm, proceed with Stage 3.

STAGE 3

6. Perform this test within approximately 5 min of the conductivity determination in Step 5, while maintaining the sample temperature at $25 \pm 1^\circ$. Add a saturated potassium chloride solution to the same water sample (0.3 mL per 100 mL of the test specimen), and determine the pH to the nearest 0.1 pH unit, as directed under pH (791).
7. Referring to the *Stage 3—pH and Conductivity Requirements* table, determine the conductivity limit at the measured pH value. If the measured conductivity in Step 4 is not greater than the conductivity requirements for the pH determined in Step 6, the water meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0–7.0, the water does not meet the requirements of the test for conductivity.

Stage 3—pH and Conductivity Requirements
(for atmosphere- and temperature-equilibrated samples only)

pH	Conductivity Requirement (μS/cm)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

Change to read:

STERILE WATER

The procedure and test limits are intended for *Sterile Purified Water*, *Sterile Water for Injection*, *Sterile Water for Inhalation*, and *Sterile Water for Irrigation*, and any other monographs which specify this section. The sterile waters are derived from *Purified Water* or *Water for Injection*, and therefore have been determined to be compliant with the *Bulk Water* requirements before being stored in the container. The specification provided represents the maximum allowable conductivity value, taking into consideration the limitation of the measurement method and reasonable container leaching. Such specification and the sampling volume choices should be defined and validated on the basis of the intended purpose of the water.

Procedure

- Obtain a sample that suitably reflects the quality of water used. Before opening, vigorously agitate the package to ho-

mogenize the water sample. Several packages may be required to collect sufficient water for analysis. ■1S (USP36)

Transfer a sufficient amount of water to a suitable container, and stir the test specimen. Adjust the temperature, if necessary, and, while maintaining it at $25 \pm 1^\circ$, begin vigorously agitating the test specimen while periodically observing the conductivity. When the change in conductivity (due to uptake of ambient carbon dioxide) is less than a net of $0.1 \mu\text{S}/\text{cm}$ per 5 min, note the conductivity.

For containers with a nominal volume of 10 mL or less, if the conductivity is not greater than ■25■1S (USP36) $\mu\text{S}/\text{cm}$, the water meets the requirements. For containers with a nominal volume greater than 10 mL, if the conductivity is not greater than $5 \mu\text{S}/\text{cm}$, the water meets the requirements.

(841) SPECIFIC GRAVITY

Change to read:

Unless otherwise stated in the individual monograph, the specific gravity determination is applicable only to liquids, and unless otherwise stated, is based on the ratio of the weight of a liquid in air at 25° to that of an equal volume of water at the same temperature. Where a temperature is specified in the individual monograph, the specific gravity is the ratio of the weight of the liquid in air at the specified temperature to that of an equal volume of water at the same temperature. When the substance is a solid at 25° , determine the specific gravity of the melted material at the temperature directed in the individual monograph, and refer to water at 25° .

Unless otherwise stated in the individual monograph, the density is defined as the mass of a unit volume of the substance at 25° , expressed in kilograms per cubic meter or grams per cubic centimeter ($1 \text{ kg}/\text{m}^3 = 10^{-3} \text{ g}/\text{cm}^3$). ■Where the density is known, mass can be converted to volume, or volume converted to mass, by the formula: volume = mass/density. ■1S (USP36)

Unless otherwise directed in the individual monograph, use *Method I*.

METHOD I

Procedure—Select a scrupulously clean, dry pycnometer that previously has been calibrated by determining its weight and the weight of recently boiled water contained in it at 25° . Adjust the temperature of the liquid to about 20° , and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25° , remove any excess liquid, and weigh. When the monograph specifies a temperature different from 25° , filled pycnometers must be brought to the temperature of the balance before they are weighed. Subtract the tare weight of the pycnometer from the filled weight.

The specific gravity of the liquid is the quotient obtained by dividing the weight of the liquid contained in the pycnometer by the weight of water contained in it, both determined at 25° , unless otherwise directed in the individual monograph.

METHOD II

The procedure includes the use of the oscillating transducer density meter. The apparatus consists of the following:

- a U-shaped tube, usually of borosilicate glass, which contains the liquid to be examined;
- a magneto-electrical or piezo-electrical excitation system that causes the tube to oscillate as a cantilever oscillator at a characteristic frequency depending on the density of the liquid to be examined;
- a means of measuring the oscillation period (T), which may be converted by the apparatus to give a direct reading of density or used to calculate density by using the constants A and B described below; and
- a means to measure and/or control the temperature of the oscillating transducer containing the liquid to be tested.

The oscillation period is a function of the spring constant (c) and the mass of the system:

$$T^2 = \{(M/c) + [(\rho \times V)/c]\} \times 4\pi^2$$

where ρ is the density of the liquid to be tested, M is the mass of the tube, and V is the volume of the filled tube.

Introduction of two constants $A = c/(4\pi^2 \times V)$ and $B = (M/V)$ leads to the classical equation for the oscillating transducer:

$$\rho = A \times T^2 - B$$

The specific gravity of the liquid is given by the formula:

$$\rho_{(L)}/\rho_{(W)}$$

where $\rho_{(L)}$ and $\rho_{(W)}$ are the densities of the liquid and water, respectively, both determined at 25° , unless otherwise directed in the individual monograph.

Calibration—The constants A and B are determined by operating the instrument with the U-tube filled with two different samples of known density (e.g., degassed water and air). Perform the control measurements daily, using degassed water. The results displayed for the control measurement using degassed water do not deviate from the reference value ($\rho_{25} = 0.997043 \text{ g}/\text{cm}^3$) by more than its specified error. Precision is a function of the repeatability and stability of the oscillator frequency. Density meters are able to achieve measurements with an error on the order of $1 \times 10^{-3} \text{ g}/\text{cm}^3$ to $1 \times 10^{-5} \text{ g}/\text{cm}^3$ and a repeatability of $1 \times 10^{-4} \text{ g}/\text{cm}^3$ to $1 \times 10^{-6} \text{ g}/\text{cm}^3$. For example, an instrument specified to $\pm 1 \times 10^{-4} \text{ g}/\text{cm}^3$ must display $0.9970 \pm 0.0001 \text{ g}/\text{cm}^3$ in order to be suitable for further measurement, otherwise a readjustment is necessary. Calibration with certified reference materials should be carried out regularly.

Procedure—Using the manufacturer's instructions, perform the measurements using the same procedure as for *Calibration*. If necessary, equilibrate the liquid to be examined at 25° before introduction into the tube to avoid the formation of bubbles and to reduce the time required for measurement. Factors affecting accuracy include the following:

- temperature uniformity throughout the tube,
- nonlinearity over a range of density,
- parasitic resonant effects, and
- viscosity, if the oscillating transducer density meters used do not provide automatic compensation of sample viscosity influence.

General Chapters

General Information

<1031> THE BIOCOMPATIBILITY OF MATERIALS USED IN DRUG CONTAINERS, MEDICAL DEVICES, AND IMPLANTS

Change to read:

This chapter provides guidance on the identification and performance of procedures for evaluating the biocompatibility of drug containers, elastomeric closures, medical devices, and implants. Biocompatibility refers to the tendency of these products to remain biologically inert throughout the duration of their contact with the body. The biocompatibility testing procedures referenced in this chapter are designed to detect the nonspecific, biologically reactive, physical or chemical characteristics of medical products or the materials used in their construction. In combination with chemical assays, these biological procedures can be used to detect and identify the inherent or acquired toxicity of medical products prior to or during their manufacturing and processing.

Preclinical testing procedures to evaluate the safety of the elastomers, plastics, or other polymers used in the construc-

tion of medical products are referenced or described in the following general chapters: *Injections* <1>, *Biological Reactivity Tests, In Vitro* <87>, *Biological Reactivity Tests, In Vivo* <88>, *Transfusion and Infusion Assemblies and Similar Medical Devices* <161>, *Elastomeric Closures for Injections* <381>, and *Containers—Plastics* <661>. Specific in vitro and in vivo testing procedures to evaluate the biocompatibility of medical products in patients are described under *Biological Reactivity Tests, In Vitro* <87> and under *Biological Reactivity Tests, In Vivo* <88>.

The procedures used to evaluate the biocompatibility of a medical product or its construction materials have been categorized as a panel of biological effects (toxicity procedures): cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity, subchronic toxicity ■(repeated),■1S (USP36) genotoxicity, implantation, hemocompatibility, chronic toxicity (extending beyond 10% of the life span of the test animal or beyond 90 days), carcinogenicity, reproductive or developmental toxicity, and biodegradation.¹ The USP general chapters referring to the toxicity procedures for these categories are indicated in *Table 1*. In addition, pyrogenicity, an area of special toxicity, is evaluated under *Pyrogen Test* <151> and under *Bacterial Endotoxins Test* <85>. There are currently no general chapters that detail ■1S (USP36) subchronic toxicity, genotoxicity, chronic toxicity, carcinogenicity, hemotoxicity, reproductive toxicity, or biodegradation testing ■2■1S (USP36) requirements.

¹ ISO document 10993-1:1997 (or latest version) entitled *Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing*.

² See OECD Guidelines for Testing of Chemicals at www.oecd.org.■1S (USP36)

Table 1. Toxicity Procedures in the USP General Chapters

Biological Effect	USP General Chapter
Cytotoxicity	<i>Biological Reactivity Tests, In Vitro</i> <87>*
Sensitization	■Sensitization Testing <1184>■1S (USP36)
Irritation or intracutaneous reactivity	<i>Biological Reactivity Tests, In Vivo</i> <88>†
Systemic toxicity (acute toxicity)	<i>Biological Reactivity Tests, In Vivo</i> <88>
■	■1S (USP36)
Implantation	<i>Biological Reactivity Tests, In Vivo</i> <88>
■	■1S (USP36)

* Additional general chapters referring to this biological effect include *Transfusion and Infusion Assemblies and Similar Medical Devices* <161>, *Elastomeric Closures for Injections* <381>, and *Containers—Plastics* <661>.

† Additional general chapters referring to this biological effect include *Injections* <1>, *Transfusion and Infusion Assemblies and Similar Medical Devices* <161>, *Elastomeric Closures for Injections* <381>, and *Containers—Plastics* <661>.

DRUG CONTAINERS

Biocompatibility of Plastic and Other Polymeric Drug Containers

Pharmaceutical containers consist of a container and a closure. Plastic containers may consist of polymers that upon extraction do not alter the stability of the contained product or do not exhibit toxicity. The biocompatibility testing requirements for drug containers are stated under *Injections* (1) and *Containers—Plastics* (661). As directed in these chapters, the plastic or other polymeric portions of these products are tested according to the procedures set forth under *Biological Reactivity Tests, In Vitro* (87). A plastic or other polymer that does not meet the requirements of *Biological Reactivity Tests, In Vitro* (87) is not a suitable material for a drug container. Materials that meet the in vitro requirements qualify as biocompatible materials without the need for further testing and may be used in the construction of a drug container. If a class designation (classes I–VI) for plastics or other polymers is desired, the appropriate testing procedures are performed as discussed in the section *In Vivo Testing and Class Designation*.

Elastomeric Closures

Elastomeric closures are closures that can be pierced by a syringe and maintain their integrity because of their elastic properties. Elastomeric materials may be composed of several chemical entities including fillers, pigments, plasticizers, stabilizers, accelerators, vulcanizing agents, and a natural or a synthetic polymer. These materials are used for manufacturing a product with the desired elastomeric physical properties, and they frequently demonstrate biological reactivity—cellular degeneration and malformation—when tested with in vitro cell cultures.

The biocompatibility of an elastomeric material is evaluated according to the two-stage testing protocol specified in the *Biological Test Procedures under Elastomeric Closures for Injections* (381). Unlike plastics or other polymers, an elastomeric material that does not meet the requirements of the first-stage (in vitro) testing may qualify as a biocompatible material by passing the second-stage (in vivo) testing, which consists of the *Systemic Injection Test* and the *Intracutaneous Test* described under *Biological Reactivity Tests, In Vivo* (88). No class or type distinction is made between elastomeric materials that meet the requirements of the first stage of testing and those that qualify as biocompatible materials by meeting the second-stage requirements. Elastomeric materials are not assigned class I–VI designation.

MEDICAL DEVICES AND IMPLANTS

Medical devices and implants, labeled nonpyrogenic, in direct or indirect contact with the cardiovascular system or other soft body tissues, meet the requirements described under *Transfusion and Infusion Assemblies and Similar Medical Devices* (161). The products listed in this chapter that meet the criteria are solution administration sets, extension sets, transfer sets, blood administration sets, intravenous catheters, dialyzers and dialysis tubing and accessories, transfusion and infusion assemblies, and intramuscular drug delivery catheters. The outlined criteria do not apply to medical products such as orthopedic products, latex gloves, and wound dressings.

The testing requirements described or referenced under *Transfusion and Infusion Assemblies and Similar Medical Devices* (161) include *Sterility*, *Bacterial endotoxins*, *Pyrogen*, and *Other requirements*. A procedure to evaluate the presence of bacterial endotoxins is set forth under *Bacterial Endotoxins Test* (85), and the limits are set in *Bacterial Endotoxins* under

Transfusion and Infusion Assemblies and Similar Medical Devices (161). For devices that cannot be tested by the *Bacterial Endotoxins Test* (85) because of nonremovable inhibition or enhancement, the *Pyrogen Test* (151) is applied. The procedures for evaluating medical devices purported to contain sterile pathways are set forth in *Sterile Devices* under *Sterility Tests* (71). A procedure for evaluating the safety of medical devices is set forth in the *Safety Test* under *Biological Reactivity Tests, In Vivo* (88).

The plastic or other polymer components of medical devices meet the requirements specified for plastics and other polymers under *Containers—Plastics* (661); those made of elastomers meet the requirements under *Elastomeric Closures for Injections* (381). As directed in these chapters, the biocompatibility of the plastic, other polymeric, and elastomeric portions of these products are tested according to the procedures described under *Biological Reactivity Tests, In Vitro* (87). If a class designation for a plastic or other polymer is also required, the appropriate testing procedures described under *Biological Reactivity Tests, In Vivo* (88) are performed.

As required for elastomeric closures, elastomeric materials that do not meet the in vitro requirements may qualify as biocompatible materials and may be used in the construction of medical devices if they meet the requirements of the *Systemic Injection Test* and the *Intracutaneous Test* under *Biological Reactivity Tests, In Vivo* (88). As required for drug containers, plastics and other polymers that do not meet the in vitro testing requirements are not suitable materials for use in medical devices.

Change to read:

IN VITRO TESTING, IN VIVO TESTING, AND CLASS DESIGNATION FOR PLASTICS AND OTHER POLYMERS

The testing requirements specified under *Biological Reactivity Tests, In Vitro* (87) and *Biological Reactivity Tests, In Vivo* (88) are designed to determine the biological reactivity of mammalian cell cultures and the biological response of animals to elastomeric, plastic, and other polymer materials with direct or indirect patient contact. The biological reactivity of these materials may depend on both their surface characteristics and their extractable chemical components. The testing procedures set forth in these chapters can often be performed with the material or an extract of the material under test, unless otherwise specified.

Preparation of Extracts

Evaluation of the biocompatibility of a whole medical product is often not realistic; thus, the use of representative portions or extracts of selected materials may be the only practical alternative for performing the assays. When representative portions of the materials or extracts of the materials under test are used, it is important to consider that raw materials may undergo chemical changes during the manufacturing, processing, and sterilization of a medical product. Although in vitro testing of raw materials can serve as an important screening procedure, a final evaluation of the biocompatibility of a medical product is performed with portions of the finished and sterilized product.

The preparation of extracts is performed according to the procedures set forth under *Biological Reactivity Tests, In Vitro* (87) and under *Biological Reactivity Tests, In Vivo* (88). Extractions may be performed at various temperatures (121°, 70°, 50°, or 37°), for various time intervals (1 hour, 24 hours, or 72 hours), and in different extraction media. The choice of extraction medium for the procedures under *Biological Reactivity Tests, In Vitro* (87) includes *Sodium Chloride Injection* (0.9% NaCl) or tissue culture medium with or without se-

rum. When medium with serum is used, the extraction temperature cannot exceed 37°. In vivo extraction medium includes the choices described under *Biological Reactivity Tests, In Vivo* <88> or the solvent to which the drug or medical device is exposed.

When choosing extraction conditions, select the temperature, solvent, and time variables that best mimic the “in use” conditions of the product. The performance of multiple tests at various conditions can be used to simulate variations in the “in use” conditions. Although careful selection of extraction conditions allows the simulation of manufacturing and processing conditions in the testing of raw materials, an evaluation of the biocompatibility of the product is performed with the finished and sterilized product.

In Vitro Testing

The procedures described under *Biological Reactivity Tests, In Vitro* <87> include an *Agar Diffusion Test* (indirect contact test), a *Direct Contact Test*, and an *Elution Test* (extraction test). The sample is biocompatible if the cell cultures do not exhibit greater than a mild reactivity (Grade 2) to the material under test, as described under *Biological Reactivity Tests, In Vitro* <87>. The *Agar Diffusion Test* is designed to evaluate the biocompatibility of elastomeric materials. The material is placed on the agar overlay of the cell monolayer, which cushions the cells from physical damage by the material and allows leachable chemicals or materials to diffuse from the elastomer and contact the cell monolayer. Extracts of elastomeric materials are tested by placing the filter paper saturated with an extract of the elastomer on the solidified surface of the agar. The *Direct Contact Test* is designed for elastomeric or plastic materials that will not physically damage cells with which they are in direct contact. Any leachable chemicals diffuse from the material into the serum-supplemented growth medium and directly contact the cell monolayer. The *Elution Test* is designed to evaluate the extracts of polymeric materials. The material may be applied directly to the tissue culture media.

The performance of either the *Agar Diffusion Test* or the *Direct Contact Test* in combination with the *Elution Test* is the preferred testing protocol. Extraction of the product or materials for the *Agar Diffusion Test* or the *Elution Test* is performed as described in the *Preparation of Extracts*.

In Vivo Testing and Class Designation

According to the injection and implantation requirements specified in *Table 1* under *Biological Reactivity Tests, In Vivo* <88>, plastics and other polymers are assigned a class designation between class I and class VI. To obtain a plastic or other polymer class designation, extracts of the test material are produced according to the specified procedures in various media.

To evaluate biocompatibility, the extracts are injected systemically and intracutaneously into mice and ■rabbits or guinea pigs■¹⁵ (USP36). According to the specified injection requirements, a plastic or other polymer may initially be graded as class I, II, III, or V. If in addition to injection testing, implantation testing using the material itself is performed, the plastic or other polymer may be classified as class IV or class VI.

Change to read:

BIOCOMPATIBILITY OF MEDICAL DEVICES AND IMPLANTS

In addition to evaluating medical products for compendial purposes according to the procedures specified under *Injections* <1>, *Sterility* <71>, *Biological Reactivity Tests, In Vitro* <87>, *Biological Reactivity Tests, In Vivo* <88>, *Transfusion and Infusion Assemblies and Similar Medical Devices* <161>, *Elastomeric Closures for Injections* <381>, and *Containers—Plastics* <661>, medical devices and implants are evaluated for sensitization, subchronic toxicity, genotoxicity, hemocompatibility, chronic toxicity, carcinogenicity, reproductive or developmental toxicity, and biodegradation as required by the regulatory agencies.

The guidance provided by the regulatory agencies indicates that the extent of testing that is performed for a medical device or an implant depends on the following factors: (1) the similarity and uniqueness of the product relative to previously marketed (“predicate”) products as considered in the *Decision Flowchart*; (2) the extent and duration of the contact between the product and the patient as described in the *Categorization of Medical Devices*; and (3) the material composition of the product as considered in the sections *Decision Flowchart* and *In Vivo Testing and Class Designation*.

Decision Flowchart

Guidance on comparing a medical device or an implant to previously marketed products is provided by the Biocompatibility Decision Flowchart (see *Figure 13*) as adapted from the FDA’s Blue Book Memorandum #G95-1. The purpose of the flowchart is to determine whether the available data from previously marketed devices are sufficient to ensure the safety of the device under consideration. As indicated by the flowchart, the material composition and the manufacturing techniques of a product are compared to those of the previously marketed products for the devices that come in direct contact with the body. In addition, the flowchart requires an evaluation of the toxicity of any unique material that has not been used in predicate devices. Responses to the questions posed in the flowchart lead to the conclusion that either the available data are sufficient or additional testing is required to ensure the safety of the product. When additional testing is required, guidance on the identification of appropriate testing procedures is provided in the section *Test Selection Matrix*.

Categorization of Medical Devices

To facilitate the identification of appropriate testing procedures, medical devices are divided and subdivided, as shown in *Table 2*, according to the nature and extent of their contact with the body. Major categories of medical devices are surface devices, external communicating devices, and implant devices. These are then further subcategorized. Some examples of medical devices and implants belonging to each of the subcategories are also presented in *Table 2*.

¹⁵■15 (USP36) Adapted from the FDA Blue Book Memorandum #G95-1 (“Use of International Standard ISO-10993. ‘Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing.’”)

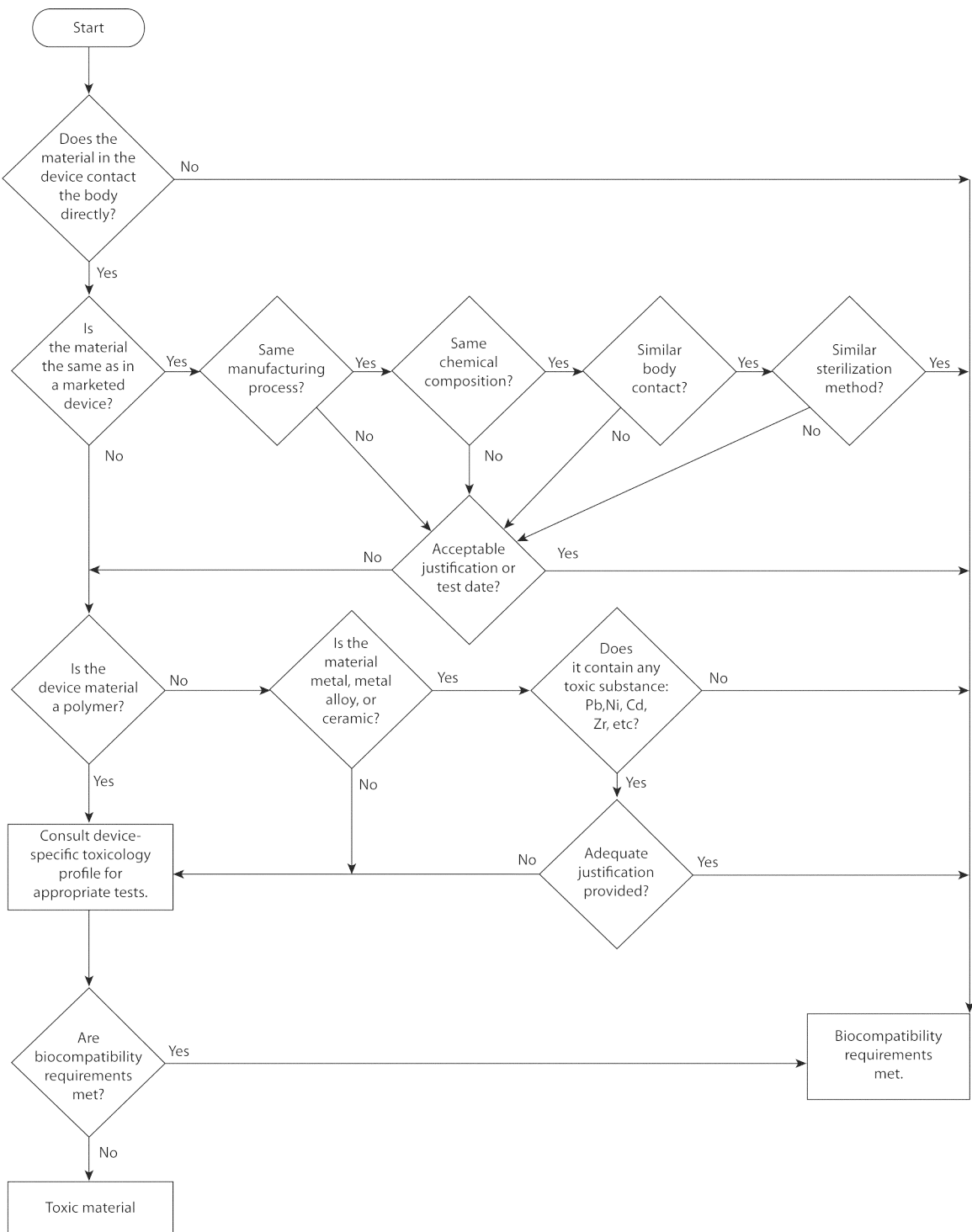


Figure 1. Biocompatibility flowchart.

Table 2. Classification and Examples of Medical Devices

Device Category	Device Subcategory	Nature or Extent of Contact	Some Examples
Surface Devices	Skin	Devices that contact intact skin surfaces only	Electrodes, external prostheses, fixation tapes, compression bandages, and monitors of various types
	Mucosal Membrane	Devices communicating with intact mucosal membranes	Contact lenses, urinary catheters, intravaginal and intrainestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gas troscopes), endotracheal tubes, bronchoscopes, dental prostheses, orthodontic devices, and intrauterine devices
	Breached or Compromised Surfaces	Devices that contact breached or otherwise compromised body surfaces	Ulcer, burn, and granulation tissue dressings or healing devices and occlusive patches
External Communicating Devices	Blood Path, Indirect	Devices that contact the blood path at one point and serve as a conduit for entry into the vascular system	Solution administration sets, extension sets, transfer sets, and blood administration sets
	Tissue, Bone, or Dentin Communicating	Devices and materials communicating with tissue, bone, or pulp and dentin system	Laparoscopes, arthroscopes, draining systems, dental cements, dental filling materials, and skin staples
	Circulating blood	Devices that contact circulating blood	Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialyzers, dialysis tubing and accessories, hemoadsorbents, and immunoabsorbents
Implant Devices	Tissue or Bone	Devices principally contacting bone or principally contacting tissue and tissue fluid	Examples of the former are orthopedic pins, plates, replacement joints, bone prostheses, cements, and intraosseous devices; examples of the latter are pacemakers, drug supply devices, neuromuscular sensors and simulators, replacement tendons, breast implants, artificial larynxes, subperiosteal implants, and ligation clips
	Blood	Devices principally contacting blood	Pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, internal drug delivery catheters, and ventricular-assist devices

Test Selection Matrix

The matrix provides guidance on the identification of appropriate biological testing procedures for the three categories of medical devices: tests for *Surface Devices* (see Table 3), tests for *External Communicating Devices* (see Table 4), and tests for *Implant Devices* (see Table 5). Each category of devices is subcategorized and then even further subdivided according to the duration of the contact between the device and the body. The duration of contact is defined as (A) limited (less than 24 hours); (B) prolonged (24 hours to 30 days); or (C) permanent (more than 30 days). The biological effects that are included in the matrix are cytotoxicity, sensitization, irritation or intracutaneous reactivity, systemic toxicity, subchronic toxicity, genotoxicity, implantation, hemocompatibility, chronic toxicity, carcinogenicity, reproductive or developmental toxicity, and biodegradation. The general chapters that contain toxicity testing procedures for these biological effects are indicated in Table 1.

Each subcategory in the matrix has an associated panel of testing requirements. Generally, the number of tests in the panel increases as the duration of the contact between the device and the body is extended and as the device or implant comes in closer contact with the circulatory system. Within several subcategories, the option of performing additional tests beyond those required should be considered on a case-by-case basis. Specific situations such as use of permanent implant devices or external communicating devices for pregnant women ■and children■ (USP36) have to be taken

into consideration in the manufacturer's decision to include reproductive or developmental testing. Guidance on the identification of possible additional testing procedures is provided in the matrix for each subcategory of medical devices.

Change to read:

GUIDANCE IN SELECTING THE PLASTIC OR OTHER POLYMER CLASS DESIGNATION FOR A MEDICAL DEVICE

To provide guidance on selecting the appropriate plastic or other polymer class designation for a medical device, each subcategory of *Surface Devices* (see Figure 2) and *External Communicating Devices* (see Figure 3) is assigned a USP Plastic Class designation (see *Biological Reactivity Tests, In Vivo* (88)). If the tests for each USP class designation are not sufficient for a specific device, the manufacturer or the practitioner must develop an appropriate set of tests. The indicated numerical class number increases relative to the duration (risk) of contact between the device and the body. In the category of *Implant Devices*, the exclusive use of class VI is mandatory. The assignment of USP Plastic Class designation is based on the test selection matrices illustrated in Tables 3, 4, and 5.

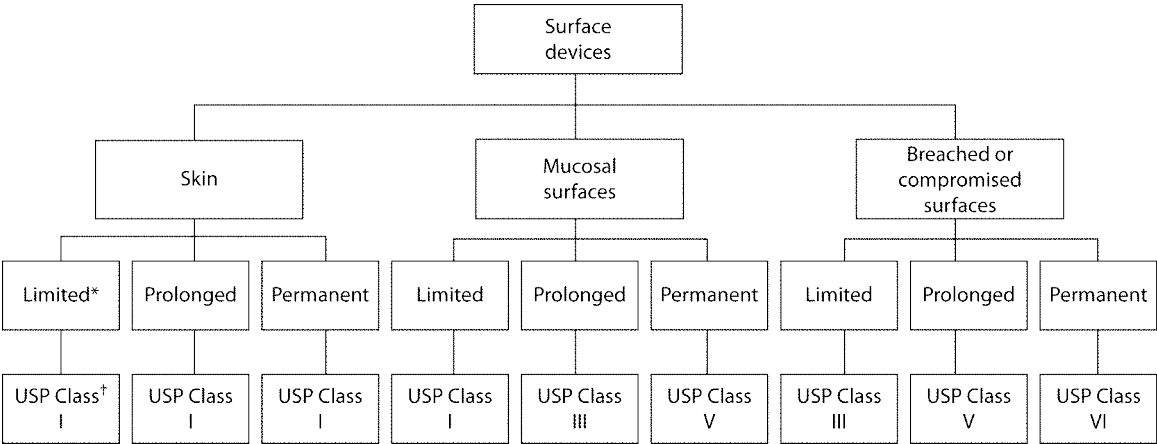


Figure 2. USP plastic and other polymer class requirements for surface devices.

* Categorization based on duration of contact: limited—less than 24 hours; prolonged—24 hours to 30 days; permanent—more than 30 days.
† USP Plastic Class designation.

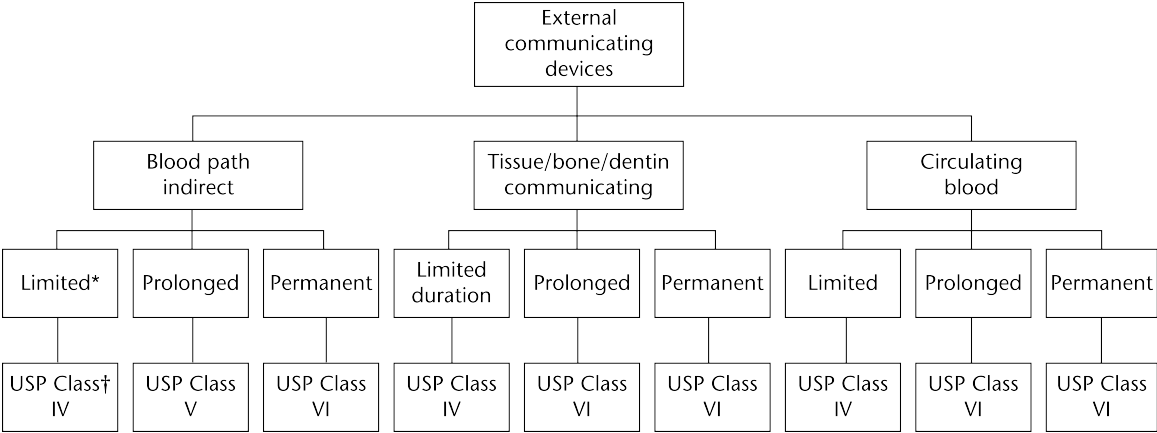



Figure 3. USP plastic and other polymer class requirements for external communicating devices.

* Categorization based on duration of contact: limited—less than 24 hours; prolonged—24 hours to 30 days; permanent—more than 30 days.
† USP Plastic Class designation.

The assignment of a plastic or other polymer class designation to a subcategory is not intended to restrict the use of higher classes of plastics or other polymers. Although the assigned class defines the lowest numerical class of plastic or other polymer that may be used in the corresponding de-

vice, the use of a numerically higher class of plastic is optional. When a device can be defined as belonging to more than one device category, the plastic or other polymer should meet the requirements of the highest numerical class.

Table 3. Test Selection Matrix for Surface Devices*

Device Categories		Biological Effect ^b											
	Con- tact Dur- ation ^a	Cyto- toxicity	Sensi- zation	Irrita- tion or Intra- cutane- ous Re- activity	Systemic Toxicity (Acute)	Sub- chronic Toxicity  ^{USP30}	Ge- no- toxic- ity	Im- plan- ta- tion	Hemo- com- pat- ability	Chro- nic Tox- ici- ty	Carci- nogen- icity	Repro- ductive or Devel- op- ment Toxicity	Bio- degra- da- tion
Sur- face De- vices	Body Contact												
	A	X	X	X	—	—	—	—	—	—	—	—	—
	B	X	X	X	—	—	—	—	—	—	—	—	—
	C	X	X	X	—	—	—	—	—	—	—	—	—
	A	X	X	X	—	—	—	—	—	—	—	—	—
	B	X	X	X	O	O	—	O	—	—	—	—	—
	C	X	X	X	O	X	X	O	—	O	—	—	—
	A	X	X	X	O	—	—	—	—	—	—	—	—
	B	X	X	X	X	O	O	—	—	—	—	—	—
	C	X	X	X	X	O	X	X	O	O	—	—	—

^a Legend A—limited (less than 24 hours); B—prolonged (24 hours to 30 days); C—permanent (more than 30 days).^b Legend X—ISO evaluation tests for consideration; O—additional tests that may be applicable.

* Adapted from the FDA's Blue Book Memorandum #G95-1 (Table 1. Initial Evaluation Tests for Consideration and Table 2. Supplementary Evaluation Tests for Consideration).

Table 4. Test Selection Matrix for External Communicating Devices*

Device Categories			Biological Effect ^b										
	Contact Duration ^a	Cyto-tox-icity	Sen-siti-zation	Irrita-tion or Intra-cutaneous Re-activity	Systemic Toxicity (Acute)	Sub-chronic Toxicity ■ ^{USP36}	Geno-toxicity	Implan-tation	Hemo-com-pat-ability	Chro-nic Toxic-ity	Cardi-no-genic-ity	Repro-ductive or Devel-op-ment Toxicity	Bio-degra-dation
Body Contact	A	X	X	X	X	X	—	—	X	—	—	—	—
	B	X	X	X	X	O	—	—	X	—	—	—	—
	C	X	X	O	X	X	X	O	X	X	X	—	—
	A	X	X	X	X	O	—	—	—	—	—	—	—
	B	X	X	O	O	O	X	X	—	—	—	—	—
	C	X	X	O	O	O	X	X	—	—	—	—	—
	A	X	X	X	X	O	—	—	—	—	—	—	—
	B	X	X	X	X	O	X	X	—	—	—	—	—
	C	X	X	X	X	O	O	X	—	X	X	—	—
External Com-mun-icating De-vices	A	X	X	X	X	—	O	—	X	—	—	—	—
	B	X	X	X	X	O	X	O	X	—	—	—	—
	C	X	X	X	X	X	X	O	X	X	X	—	—

^a Legend A—limited (less than 24 hours); B—prolonged (24 hours to 30 days); C—permanent (more than 30 days).^b Legend X—ISO evaluation tests for consideration; O—additional tests that may be applicable.

* Adapted from the FDA's Blue Book Memorandum #G95-1 (Table 1. Initial Evaluation Tests for Consideration and Table 2. Supplementary Evaluation Tests for Consideration).

Table 5. Test Selection Matrix for Implant Devices*

Device Categories		Biological Effect ^b												
Body Contact	Con- tact Dur- ation ^a	Cyto- tox- icity	Sen- sit- iza- tion	Irritation or Intra- cutan- eous Re- activity	System- ic Toxicity (Acute)	Sub- chro- nic Tox- icity <small>§15 (USP36)</small>	Geno- toxicity	Implan- tation	Hemo- com- pat- abili- ty	Chro- nic Toxic- ity	Carci- no- genic- ity	Re- pro- duc- tive or Devel- op- ment Toxici- ty	Bio- degra- da- tion	
		A	X	X	X	O	—	—	—	—	—	—	—	—
		B	X	X	O	O	O	X	X	—	—	—	—	—
		C	X	X	O	O	O	X	X	—	X	X	—	—
		A	X	X	X	X	—	—	X	X	—	—	—	—
		B	X	X	X	X	O	X	X	X	—	—	—	—
		C	X	X	X	X	X	X	X	X	X	X	—	—

^a Legend A—limited (less than 24 hours); B—prolonged (24 hours to 30 days); C—permanent (more than 30 days).

^b Legend X—ISO evaluation tests for consideration; O—additional tests that may be applicable.

* Adapted from the FDA's Blue Book Memorandum #G95-1 (Table 1. Initial Evaluation Tests for Consideration and Table 2. Supplementary Evaluation Tests for Consideration).

Add the following:

«1106» Immunogenicity Assays— Design and Validation of Immunoassays to Detect Anti- Drug Antibodies

INTRODUCTION AND SCOPE

Anti-drug antibodies (ADA) can be induced when animal or human immune systems recognize a protein drug product as foreign. The administration of biopharmaceuticals can elicit product-specific ADA, and various types of ADA responses can develop in either nonclinical or clinical studies. [NOTE—A list of regulatory documents, white papers, and other relevant references is contained in the *Appendix*.] Although the main focus of this chapter is ADA immunoassay design and validation, the chapter also includes discussion of an overall risk-based immunogenicity assay testing strategy that includes preclinical and clinical studies.

ADA assay results are directly influenced by assay design, assay reagents, how the assay is run, what samples are run in the assay (timing of sample collection, etc.), and how assay data are analyzed. In fact, it essentially is impossible to compare the results of studies that use different ADA assays. Guidance, such as this general information chapter, recommending best practices and considerations for ADA assay development helps ensure that the assays produce results that are meaningful for patient safety and product efficacy.

The primary concern with unintended or unwanted immunogenicity of biological products is whether antibodies produced by patients receiving the product lead to some form of clinical response (e.g., an effect on safety or efficacy). The utility and interpretation of preclinical toxicology studies also can be influenced by the presence of ADA.

The pharmacokinetics (PK) or the pharmacologic activity of the drug can be altered by ADA that either enhance or reduce the clearance of the drug, alter bioavailability, or inhibit or exacerbate the pharmacological action of the drug. If an endogenous counterpart of a drug exists, ADA that inhibit the activity of the product also can bind to and cross-react with an endogenous protein counterpart of the product, potentially leading to a deficiency syndrome. Under some circumstances, ADA can form immune complexes that can induce serum sickness-type clinical responses. Moreover, IgE isotype ADA responses can result in anaphylaxis.

Immunogenicity assessments are playing an increasing role in biopharmaceutical development as part of Product Quality Risk Assessments (PQRAs) and the assessment of the criticality of quality attributes (as described in ICH Q8 and Q9). They also play a role in the demonstration of process and product comparability after manufacturing process changes. Often the manufacturing process for a biological therapeutic will be refined during clinical development, and often changes occur after the sponsor obtains marketing authorization. Such changes, however minor, potentially could affect the bioactivity, efficacy, or safety of a biotherapeutic, and immunogenicity is a key consideration. Changes in the levels and types of degradation products (oxidized, deamidated, aggregates, or others), isoforms of the protein, and process-related impurities such as host cell protein and DNA could affect immunogenicity and warrant closer evaluation.

FACTORS THAT AFFECT THE IMMUNOGENIC POTENTIAL OF A THERAPEUTIC PROTEIN

Many factors can influence whether administration of a biological product will induce an immune response in the recipient, including the structure of the protein product itself, product variants, product formulations, the immune status and genetic makeup of the patient, and the dosing route and regimen used in the clinic.

Protein Structure

The primary amino acid structure of the product and its variants can determine if there are immunogenic epitopes that the patient's immune system recognizes as foreign, leading to an immune response. Amino acid sequences that are not found in human proteins and thus could be recognized as foreign by the human immune system (e.g., those derived from a nonhuman cell line or created by protein engineering, e.g., fusion proteins) not surprisingly can induce an immune response in humans. In addition, chemical modification of amino acids (e.g., oxidation or deamidation) may result in a sequence that can stimulate an immune response, although few data to date have confirmed such occurrences following administration of therapeutic proteins. Truncation of the protein could expose amino acid motifs (neopeptides) not normally exposed in the native protein, stimulating an immune response.

In general, glycosylation does not appear to play a major role in the induction of immune responses to biological products, although nonhuman (e.g., murine) or nonmammalian (e.g., products derived from plants) glycosylation can induce immune responses. An example is a human monoclonal antibody that contained a terminal galactose- α -1,3-galactose because of posttranslational modification by its murine production cell line. This antibody was antigenic and caused severe hypersensitivity reactions in presensitized individuals bearing cross-reactive IgE. There was no evidence that this glycan induced primary immune reactions in naïve (i.e., not presensitized) individuals. Such examples are rare. In fact, in many cases complex carbohydrates may prevent or reduce the antigenicity of immunogenic proteins by shielding epitopes from binding antibodies.

Aggregated protein has been shown to induce immunogenicity in animal models. Proposed mechanisms of action include either presentation of high molecular weight, repeating subunits (multimers) directly to B-cells thereby inducing a T-cell-independent response or by inducing a T-cell-dependent response via enhanced antigen presentation. Addition of polyethylene glycol (PEG) molecules (PEGylation) to recombinant therapeutics has been attempted in order to attenuate immunogenicity and antigenicity of recombinant proteins by limiting exposure of epitopes. Although no clear evidence establishes that the immunogenicity of proteins is diminished by PEGylation, some clinical data suggest that PEGylation can limit antibody binding (i.e., antigenicity) to the protein backbone. PEG itself can be immunogenic and anti-PEG antibodies should be monitored, especially in subjects with known PEG hypersensitivity. In fact, a background level of anti-PEG antibodies is present in the general population, leading to the requirement to develop an anti-PEG antibody assay as well as an ADA assay during the clinical development of PEGylated products.

Process-Related Impurities

Process-related impurities such as endotoxins, host cell DNA, or proteins can act as adjuvants and can provoke an immune response by evoking danger signals via activation of immune cellular receptors such as Toll-like receptors. Some postulate that leachables from primary packaging components also can act as immune stimulators or affect the higher-order structure of the protein product and in-

duce an immunogenic response, although firm data are not yet available.

Immune Status of the Patient

The ability of the patient's immune system to recognize and respond to a protein product can dictate the level of immune response. Patients who are taking immunosuppressive drugs such as glucocorticoids, cyclosporine, or methotrexate may have a lower likelihood of immune response to a protein product despite its immunogenic potential. Conversely, autoimmune diseases and inflammation may involve the overactivation of an immune system so that a product's level of immunogenicity may be much greater than one would anticipate. The pharmacologic activity of the protein therapeutic itself should also be taken into account. Some protein therapeutics directed against B-cell antigens can deplete peripheral B-cells. Conversely, other protein therapeutics may have immune-modulatory activities, e.g., altering patterns of T-cell trafficking. These activities may affect an individual patient's or a patient population's ability to mount an immune response to a protein product.

A patient's immune status should also be considered when the patient exhibits specific pre-existing ADA, cross-reacting ADA (for example, in the case of murine- or plant-derived products), or antibodies against production cell line-related impurities that might induce a clinical response.

Genetic Background of the Patient

Molecules that recognize and present protein-derived peptides to the adaptive immune system—the human leukocyte antigen or major histocompatibility antigen molecules—show considerable genetic diversity between individuals and between populations in different parts of the world. This diversity is one reason why different patients may have different immune responses to the same product. Consequently, if clinical studies include only a population of limited genetic diversity, then the immunogenicity profile of a protein therapeutic in that population may not reflect its immunogenicity profile in the larger, more diverse population that would be exposed to product after approval.

Dose and Route of Administration

The way a therapeutic protein product is used can influence its potential for immunogenicity. Different routes of administration appear to have different effects on immunogenicity, and subcutaneous injection generally is perceived to be a more immunogenic route of exposure than is intravenous administration. The dosing regimen also can influence immunogenicity. A protein therapeutic that typically is administered one time as a single dose (e.g., a thrombolytic protein) is less likely to induce an immune response than is a protein therapeutic that is used in a multiple-dose regimen because the immune system usually requires a prime followed by a boost to ensure a robust response. Patients may have pre-existing sensitization even without any known exposure to a therapeutic protein product, and they may exhibit adverse clinical responses on first exposure. However, products with long half-lives or those that are particularly immunogenic (e.g., those with multiple T-cell epitopes) have been shown to induce ADA after a single injection. A chronic dosing regimen has a greater chance of inducing an immune response because the immune system receives multiple exposures to the product and this can lead to a strong memory T-cell response.

Another regimen that has caused ADA with clinical sequelae is one whereby a product is given for a short period of time, stopped, and then introduced again only after a long lag period. This has the effect of priming the immune system, and the reintroduction can cause immune-related events such as allergic responses. The use of chronic dosing

on a regular basis, although it repeatedly provides the drug product, appears to avoid such hyper-responsiveness by inducing some form of tolerance.

DETERMINATION OF PRECLINICAL AND CLINICAL IMMUNOGENICITY

Preclinical: Relevance and Scope of Preclinical Immunogenicity

The immunogenicity of many biotherapeutics is greater in preclinical studies and has low predictive value for humans because an immune response to human or humanized proteins tends to be greater in animals than in humans because of the perceived foreignness of the protein in animals and the absence of an endogenous biological counterpart. Even though detection of ADA in animals may not be clinically relevant, researchers must assess ADA for the interpretation of the required toxicity data necessary for regulatory submissions (see ICH S6R1 in the *Appendix*).

Generally ADA assessments, PK data, and pharmacodynamic (PD) data aid in the interpretation of the results and validity of animal toxicology studies. In some instances preclinical immunogenicity data also can be used to compare the relative immunogenicity of products before and after manufacturing changes, although only with the grossest of changes in relative immunogenicity does this appear to be meaningful. Preclinical studies, particularly in higher animal species, are typically not statistically powered to draw conclusions on relative immunogenicity but, when they can, it should be recognized that differences in MHC restriction and natural immune tolerance of animals versus humans may not permit translation of such information to effects in humans. Furthermore, it should also be acknowledged that strains of preclinical species are limited in genetic diversity compared to the human population.

ADA may alter exposure to an active drug by blocking the therapeutic agent from binding to the target or by accelerating the clearance of the therapeutic agent from circulation, resulting in reduced exposure. ADA may increase the half life of biologic drugs and with this the exposure if the drug-ADA complex is still bioactive. Typically, samples should be collected for possible ADA analysis from all preclinical safety studies in which animals are exposed to the drug for more than 7 days (see references in the *Appendix* for more information). Because the key consideration for including immunogenicity analysis in nonclinical studies is to demonstrate the exposure to the drug for the duration of the study, this also can be achieved by demonstrating drug-mediated modulation of a PD marker. In addition, an absence of an effect on the serum concentration or PK profile of the drug also can indirectly demonstrate the absence of detectable effects of an ADA on drug exposure. However, in some situations the development of an ADA may not significantly affect the clearance of the drug, but instead the ADA may affect the drug's binding to and activity at the target (e.g., anti-idiotypic antibodies). Therefore, lack of an effect on a PD marker and/or on PK also should be considered to ensure activity is not affected by the ADA.

For most nonclinical studies, samples from various phases of the study should be collected, banked, and analyzed with regard to any observed pharmacological or toxicological changes. In fact, most nonclinical toxicology studies do not evaluate the kinetics of ADA development, and samples for the assessment of ADA usually are taken at baseline, end of treatment, and end of recovery periods.

Analyses of samples taken during the dosing phase also can be performed if unusual PK data or toxicological findings are observed at the end of the study. In this case it needs to be taken into consideration that analysis of samples taken during the dosing phase may be complicated by drug interference. Therefore, it is important to take samples

at appropriate time-points (e.g., before the next dose) and to have suitable assays with high drug tolerance in place. In some instances when a soluble target may be present in the circulation, understanding of ADA level (titers or relative mass units) can facilitate the interpretation of toxicological findings.

A risk-based approach should be used to determine if further characterization (e.g., demonstrating neutralizing activity) is necessary for preclinical studies. Factors such as the presence of endogenous counterparts, utility of a PD marker, or the PK assay may affect this decision. If data from a neutralizing antibody assay (NAb) are deemed necessary, then this assay could be either a target-binding inhibition immunoassay or cell-based assay, irrespective of the risk level. Immunogenicity evaluation and study data interpretation typically require serial sampling and analysis of serum samples for PK, PD, and ADA. Such repeated and frequent sampling may not be feasible when researchers conduct studies using rodents, particularly mice. In such cases, the study can be designed to allow discrete analyses of toxicity, PK, PD, and ADA endpoints from similarly treated cohorts of mice with sample collection at similar study time points to allow inferential analysis of effects observed across treatment groups.

Clinical: Relevance and Scope of Immunogenicity Assessments

In clinical studies, ADA detection and characterization is important to understand the safety and exposure and efficacy profile of the therapeutic. Typically, the ADA analysis strategy in clinical studies involves a screening assay for binding antibodies then a confirmatory assay, followed by further characterization in NAb. Immunogenicity data from clinical studies generally are analyzed in the context of their relevance to the PK and PD of the therapeutic and on adverse events. For replacement therapies (e.g., enzyme-replacement therapies, blood clotting factors, and erythropoietin), a comprehensive monitoring program should be designed based on ADA detection combined with multiple safety parameters to monitor the potential for serious adverse events.

Researchers should consider the kinetics of the appearance of ADA during clinical studies because this can affect not only ADA detection but also the potential clinical sequelae. Some products induce antibodies rapidly, but other biotherapeutics can take years before an immune response is detected or can be correlated to any clinical sequelae. Investigators also should consider whether an antibody response is transient or persistent. Therefore, understanding the kinetics of ADA appearance is important. This goal can be achieved by carefully selecting ADA sample collection times and taking care in developing the ADA assay for clinical studies. Samples should be collected during each phase of the study (pretreatment, during treatment, and during any washout phases). The sensitivity and drug tolerance of the ADA assay also must be appropriate for the intended use of the assay. For example, when products have long terminal half-lives (e.g., monoclonal antibodies) scientists should develop ADA assays that are capable of detecting ADA in the presence of product levels that are expected to be present in patient test samples. In addition, during the design of ADA sampling plans, researchers should consider the appropriateness of obtaining samples after a washout period.

The number of patients assessed for ADA in clinical trials and the duration and timing of ADA sample collection are critical factors to understand the incidence and clinical impact of ADA. Other factors may confound ADA analysis, including the nature of the therapeutic itself, the presence of pre-existing cross-reactive antibodies, rheumatoid factors, heterophilic antibodies, soluble targets, or ligands. Samples should be taken to assess the levels of these interfering fac-

tors in serum (and other PD markers as applicable) at the same time as ADA samples.

Besides determining the presence of binding antibodies, clinical immunogenicity assessments typically include further characterization of positive samples in titer assays as well as in NAb to determine the potential effect of ADA levels to neutralize the drug's effect or to mediate safety events. In addition, understanding the kinetics of ADA and NAb development by detection of ADA in sequential samples taken throughout the study phases and elucidation of the ADA immunoglobulin class(es) and subclass(es) may aid in better understanding of patient- and treatment-related factors and the mechanisms by which the therapeutic induces ADA development.

RISK-BASED APPROACH TO ASSESSING IMMUNOGENICITY AND ITS CONSEQUENCES

Assessing the Potential Risk of Product-Specific Immunogenicity

The concept of risk is defined in ICH Q9 as the combination of the probability of occurrence of *harm* and the *severity* of that harm. In relation to pharmaceuticals, the protection of the patient by managing the risk to safety should be considered of prime importance and thus risk assessments of product-induced immune responses should focus on the potential severity of clinical consequences from ADA responses rather than the probability of occurrence of ADA responses. A few patients with severe or life-threatening ADA-related side effects are of more concern than many ADA-positive patients who have no clinical consequences. Risk mitigation should also be factored into the overall risk-assessment process (e.g., elimination of clinical impact by co-medication).

Although ADA testing strategies can be based on immunogenicity risk assessment, this may not always be feasible during early drug development when reliable assays may not be available.

ADA-induced safety events can range from mild side effects to life-threatening conditions. The potential severity of the consequences of an ADA response should be considered as early as possible. *Table 1* summarizes some but not all of the risk factors that may influence the severity of clinical consequences from an ADA response.

Table 1. Factors That May Influence the Severity of ADA-Related Clinical Sequelae

	Lower Risk ¹	Medium Risk	Higher Risk
Presence of an identical endogenous counterpart (includes families of proteins that share domains)	No endogenous counterpart (e.g., Botulinum toxin)	Redundant counterpart (e.g., interferons or growth hormones)	Nonredundant counterpart [e.g., erythropoietin or megakaryocyte growth and development factor (MGDF)]
Presence of a structurally related endogenous molecule or domain	No structurally related endogenous molecule or domain	Medium structurally related endogenous molecule or domain exists	Highly structurally related endogenous molecule or domain exists

¹ Risk is a consequence of both severity and frequency.

Table 1. Factors That May Influence the Severity of ADA-Related Clinical Sequelae (Continued)

	Lower Risk ¹	Medium Risk	Higher Risk
Patient's disease state	Life-threatening	Moderate-to-severe	Mild
Potential clinical consequences of immunogenicity	No clinically meaningful impact on safety or efficacy	Manageable impact to safety and/or efficacy	Extensive clinical influence on safety or loss (or dramatic increase) of efficacy

¹ Risk is a consequence of both severity and frequency.

A number of factors may contribute to the incidence of an ADA response, and some but not all of these factors are shown in Table 2. During an immunogenicity risk assessment the factors shown in Table 2 should be considered in conjunction with those in Table 1. The clinical consequences of immunogenicity are unpredictable, even with the risk assessments outlined above.

An immunogenicity risk assessment is of real value only when all the factors that influence the likelihood and severity of a potential immune response are carefully considered. Risk assessments should be done in a cross-functional manner, including input from clinicians, safety assessment, PK, bioanalytical scientists, as well as process scientists. Consultations with regulators and clinical safety monitoring boards also may be helpful and should be carried out iteratively during the product development process as clinical data are obtained.

ADA-mediated clinical sequelae and ADA incidence rate are separate entities, but the two factors are interrelated because the number of patients with ADA-mediated serious adverse events may rise with a higher ADA incidence rate.

Table 2. Factors That May Influence ADA Incidence

	Lower Incidence	Medium Incidence	Higher Incidence
Circulating level of endogenous counterpart	Abundant	Scarce	None
Patient's immune status	Suppressed	Normal	Activated
Exposure: dosing regimen or frequency	Single dose	Chronic (maintenance) Multiple dosing	Episodic dosing
Route of administration	Intravenous or oral	Subcutaneous, intramuscular, mucosal (non-inhalational)	Intradermal or inhalational

Table 2. Factors That May Influence ADA Incidence (Continued)

	Lower Incidence	Medium Incidence	Higher Incidence
Product Characteristics	Lowest levels (or absence) of product or process-related impurities (e.g., aggregates or denaturation, fragmentation)	Intermediate levels of product- or process-related impurities, and potential epitope content	Higher levels of product- or process-related impurities (e.g., aggregates; denaturation, fragmentation)
	Molecular integrity of active substance maintained		Higher level of antigenic epitopes (derived from murine cell lines, contains novel mutated sequences, etc.)
	No or low content of potential T-cell epitopes		Mechanism of action: immune activation
	Mechanism of action: e.g., immunosuppressant		

Risk-Based Approach to ADA Testing Strategy

The ADA testing strategy should be based on an immunogenicity risk assessment. Appropriately designed, validated, and executed immunogenicity assays and testing schemes provide the data that make risk assessments possible and predict the eventual outcome for patients. The frequency of sampling, neutralizing activity assessments, and qualitative or quasi-quantitative measurements may all depend on perceived risk.

In clinical studies, patient safety is of primary concern, and the extent of ADA characterization necessary depends on the potential risk of ADA-related sequelae. The type of drug should also be taken into account. For example, for a multicomponent fusion protein that contains at least one component with a potentially high risk of adverse events, a domain-mapping method (i.e., reactivity of ADA with individual components) is recommended.

Generally, more extensive ADA testing and characterization should be applied if the risk of clinical adverse effects is high. Samples should be analyzed and characterized based on the timing and incidence of the ADA response as well as the occurrence and severity of clinical side effects. A higher risk of ADA incidence normally does not warrant extensive characterization of ADA, and usually the risk of clinical consequences drives the bioanalytical strategy. Nevertheless, some investigations may be driven by the need to understand the cause of a high ADA incidence (e.g., the reactivity of ADA with aggregated versus nonaggregated drug).

The following step-wise, risk-based testing strategy can be refined depending on the product's level of risk and during the design of the clinical studies to ensure that the maximum amount of data can be gained, including correlations to PK, PD, etc.

Step 1: Develop ADA methods that are fit for purpose and are consistent with current industry best practices and regulatory guidance. Incorporate baseline and postdose ADA testing into the clinical study design, together with concurrent testing for PK plus any relevant PD, safety, or efficacy

markers that will facilitate interpretation of ADA data. The analysis of results from ADA testing should be built into study analysis plans.

Step 2: Test all pre- and post-dosing samples for ADA. Two important tests that should be carried out in all cases are the ADA screening assay and the drug inhibition or immunoglobulin depletion confirmation assay. Report as negative any ADA results below the assay cut-point and with drug levels below the interference levels, as well as those that test negative in the confirmatory assay. Test methods that are capable of sensitive ADA detection despite the presence of trough levels of drug are desirable. In their absence, samples containing drugs above the interference levels should be reported as inconclusive with a statement of possible drug interference. In such cases, ADA analysis could be performed later following a drug washout period to reach a conclusive result (refer to the section *Relative Sensitivity* of this chapter for further information). For the confirmed positive samples, ADA levels should be estimated, preferably by titration, but they can be reported in terms of relative mass units. Certain mass-based technology platforms may necessitate the use of relative mass units.

Step 3: Samples deemed positive in *Step 2* should be tested for neutralizing ability and potentially other characteristics, depending on the risk assessment. In high-risk situations, NAb activity should be measured, typically using a cell-based assay. Depending on the drug's mechanism of action, sometimes a ligand-binding NAb assay format can be used if it is adequately proven to specifically detect NAb. Concurrently generated PK/PD/safety or biomarker data should be used to help interpret the clinical relevance of neutralizing antibody activity. In addition, determination of ADA isotypes and affinity may be helpful in the overall assessment of the immune response. Allergic reactions associated with drug administration may necessitate measurement of drug-specific IgE, although detection may depend on the sampling scheme and method design.

DESIGN OF IMMUNOASSAY-BASED TEST METHODS

Immunoassay methods for ADA detection generally are complex and require a broad understanding of multiple technical challenges. Screening assays that serve as the key first step in the immunogenicity testing scheme are designed to have a certain false positive (rather than false negative) rate in order to maximize the sensitivity for detecting ADA. In addition, using a risk-based approach, it is more appropriate to have 5% false positives rather than false negatives during this initial screening phase. Typically, positive screening samples are confirmed to contain drug-specific ADA in confirmation assays before the determination of the level of ADA (titers) or any additional characterization.

Screening Assays

In their simplest form, screening ADA assays immobilize the therapeutic protein on a microtiter plate or onto beads to capture ADA (solid phase) or co-incubate a labeled therapeutic protein at a predetermined concentration with the sample containing ADA (solution assay). The bound polyclonal ADA is then detected using a labeled secondary reagent or labeled drug. Limiting the number of wash steps or reducing wash fluid dispensing rates may increase the detection of antibodies with fast off-rates on assay platforms that use wash steps. Generally, screening assays are designed to detect classes of antibodies that may be most relevant to the product's route of administration, e.g., IgA for mucosal routes of administration. Although the most common ADA raised against protein therapeutics are of the IgM and IgG isotypes, other isotypes of ADA including IgE and IgA may require detection based on the clinical response

and the route of product administration. In addition, depending on how rapidly ADA responses develop and the half-life of the therapeutic, it may be feasible to detect the development of ADA initially of the IgM isotype that later affinity matures to an IgG isotype following repeat administration of product.

Because screening assays serve as the first step in the immunogenicity testing program, these assays generally are configured to have moderate throughput and often are automated. The various technology platforms used to develop screening immunogenicity assays have inherent strengths and weaknesses as outlined in *Table 3*. Development of a bioanalytical strategy to use a certain technology platform for assay development should take into consideration the nature of the product (e.g., a therapeutic protein or a monoclonal antibody), potential sources of interference in the assay (e.g., therapeutic concentration anticipated in patient samples, soluble target based on co-medications, and biology), and disease-specific interfering or cross-reacting factors (e.g., rheumatoid factor).

In addition, analysts should consider whether the method does not result in an underestimation of ADA-positive samples because the ADA binding epitopes on the capture reagent are blocked with a tag or by coating on plates or beads. Another point for consideration in the design and development of an ADA assay is the adaptability of the test for both nonclinical and clinical matrices. Although most assay formats can transfer readily from nonclinical to clinical use, there are exceptions. Further, clinical ADA assays should be qualified or validated for use with samples collected from a similar patient population. Here again, although most ADA screening assays may not show unique matrix interferences between one disease matrix and another, there may be exceptions. Immunoassays used for ADA detection generally are quasi-quantitative methods because standardized, species-specific (especially human) polyclonal ADA calibrators generally are not available. The positive controls, typically developed in-house as hyperimmune serum in animals or by phage display serve as surrogates for the drug-induced ADA in treated patients.

As depicted in *Table 3*, some of the more common assay formats currently in use for development of screening assays include plate-based or bead-based enzyme-linked immunosorbent assays (ELISA; see also USP general chapter *Immunological Test Methods—Enzyme Linked Immunosorbent Assays (ELISA)* (1103)) with colorimetric, fluorometric, or luminescent read-outs, plate-based or solution-phase electrochemiluminescent (ECL) or ELISA assays, surface plasmon resonance assays (SPR; see also USP general chapter *Immunological Test Methods—Surface Plasmon Resonance* (1105)), or bilayer interferometry assays, and radioimmunoassay (RIA). In order to differentiate positive from negative responses, assay cut-points are statistically determined using samples collected from the target population. The assay cut-point also helps to determine the assay sensitivity. An incorrectly established cut-point may result in false negatives or too many false positive responses that should be ruled out as drug-specific responses in the confirmation assay. Assay performance typically is optimized during development by evaluation of the following parameters: sensitivity (lowest amount of detectable antibody in a sample demonstrated using surrogate controls); specificity (likely detection of a true positive rather than a nonspecific interaction); precision (reproducibility of results from multiple analyses); interference (interfering substances in sample matrix, including the administered drug, that affects assay sensitivity); and stability and robustness (likelihood of optimal assay performance over time). After optimizing these parameters, analysts typically validate the method for its intended use. If the initial assay cannot meet the performance goals (e.g., because of poor sensitivity or high backgrounds), then analysts should either improve and validate the first assay format again or develop and validate more than one assay format.

Table 3. Advantages and Disadvantages of Various Assay Types Currently Used to Assess ADA

Assay Type	Advantages	Disadvantages
Direct/Indirect ELISA	High throughput	Potential for high background
	Readily available	May not be specific
	Easy to automate	Utility depends on capability to detect different Ig subtypes
	Inexpensive	Drug tolerance lower for solid-phase ELISAs
	Readouts can increase sensitivity (e.g., electrochemiluminescence)	Excessive washes can decrease detection of low-affinity ADA
	Drug tolerance higher for solution-phase ELISAs	
Bridging Format	Low background	Difficult to confirm presence of IgM
	Highly specific	Need to label product
	Readily available	Reduced ability to detect low-affinity antibodies and IgG ₄ because of single-arm binding between bound ligand and detector
	Easy to automate	
	Inexpensive	
	Format can be used across species and detects all isotypes	
Surface Plasmon Resonance/Biolayer Interferometry Assays	Can be used across detection platforms (colorimetric, electrochemiluminescence, etc.)	
	Flexibility to characterize immune response (concentration and relative affinity)	Expensive technology
	Higher drug tolerance and can detect low-affinity antibodies	Limited suppliers
Radioimmuno-precipitation Assays	Inexpensive	Moderate throughput
	Highly sensitive	Radioactive waste
	Better for high-affinity antibodies	Need to frequently requalify radio-labeled reagents because of short half-life
		Utility depends on capability to precipitate all relevant antibody present
		Can be less useful for low-affinity antibodies

Confirmatory Assays

Samples that are positive in the screening assay usually are confirmed in a second assay that includes adding a certain fold excess of the therapeutic. This is intended to demonstrate that a positive signal seen in the ADA screening assay is caused by the presence of drug-specific antibodies. Because the cut-point for the screening assay is set to result in the detection of approximately 5% false positives,

the confirmatory assay is used to rule out the false positive samples from further analysis. Multiple options are available for performing confirmatory assays. Usually a soluble drug is added to the sample and should compete with the plate-bound immobilized drug for binding to sample ADA. A specific interaction to a soluble drug results in a decrease in the assay signal. As with the screening assay, the cut-point for the confirmation assay is established statistically. Verification of the presence of drug-specific antibody can also be performed using an orthogonal method on a different assay platform that may have different nonspecific binding profiles. Analysts should take care while adopting this approach to ensure an adequately sensitive assay in order to avoid a false negative reaction. Finally, the specificity of ADA to a drug can also be confirmed by depleting all immunoglobulin from a sample (e.g., using a Protein A or G column) followed by reanalysis of the depleted sample. In the latter approach, the depleted sample scores negative in the assay if an antibody caused the original signal. Validation of the confirmatory assays helps ensure that the results from the confirmatory assay are appropriately interpreted.

Characterization Assays

Following screening and confirmation, the relative level of ADA in a positive sample is assessed by titration. The most common approach is to serially dilute the sample and report the reciprocal of the highest dilution factor at which the sample tests positive, or the titer of the sample. The higher the sample dilution (and therefore the ADA titer value), the higher is the concentration of circulating ADA in that sample. This approach has been used historically to report serological data from vaccine studies. Another less frequently used approach is to express the amount of ADA in the sample in mass units relative to a surrogate standard. Although this approach has the advantage of relating the amount of antibody in the sample to assay sensitivity, analysts should recognize that the calibrator may not be representative of the polyclonal ADA responses under measurement.

Traditional approaches to dilutional linearity testing do not apply to ADA assays. However, when analysts express ADA data in terms of titer values, they also should demonstrate that the positive control(s) displays reasonable (relative) linearity of dilution.

In addition to performing titration, analysts routinely characterize positive ADA samples in neutralization assays to determine the in vitro effect of ADA that might reflect the in vivo biological or pharmacological activity of the therapeutic product. Additionally, the isotype(s) of the ADAs also can be analyzed. Isotype(s) identification is sometimes performed in a multiplexed manner. Using one fluorescent multiplex platform, analysts mix each sample with multiple secondary reagents that are specific to different immunoglobulin isotypes and are labeled with unique fluorochrome labels.

An SPR-based platform also can be used for this purpose (also see *Immunological Test Methods—Surface Plasmon Resonance* (1105)). The isotype of an ADA can be determined by observing binding of isotype-specific reagents (such as an anti-human IgG₁ Ab) to the ADA that has been captured by immobilized drug. Analysts should take care when identifying and validating the isotype-specific reagents because unexpected cross-reactivity often is observed. Isotyping can help understand the maturation of the immune response. For example, an ADA response that is comprised solely of IgM antibodies is an immature immune response without T-cell involvement and may or may not progress further. In contrast, an immune response comprised of IgG₁ and IgG₄ antibodies represents a more mature response that has already engaged more components of the immune system. ADA titration and characterization assays are validated routinely using many of the same parameters as screening and confirmation assays to ensure consistent assay performance.

VALIDATION OF IMMUNOASSAYS

Method validation is a process of demonstrating, by the use of specific laboratory investigations, that the performance characteristics of an analytical method are suitable for its intended use (see also USP general chapter *Validation of Compendial Procedures* (1225)). The level of method validation depends on the stage of product development and the risks associated with the product. A partial validation involving assessments of method sensitivity, specificity, and precision requirements with less emphasis on robustness, reproducibility, and stability may be adequate for the earlier stages of clinical development (Phase 1–Phase 2 studies), whereas fully validated methods are required for pivotal and postmarketing studies.

Validation of an assay before use of the method for sample bioanalysis is called *pre-study validation*, and amendments to this process may be made between studies. This process maps out the performance characteristics of the assay and should demonstrate that the method is suitable for its intended purpose when it is subsequently applied to study samples. In contrast, *in-study validation* refers to the monitoring of assay performance during study-phase applications of the assay in order to ensure that the assay remains valid and that the resulting bioanalytical data are reliable.

Reliable performance of the assay also depends on all the elements spanning bioanalytical testing and data manipulation, such as assay reagents, analysts, equipment, and computer programs. In essence, the assay is a system comprising several elements other than assay steps and reagents alone. Pre-study validation therefore establishes system suitability (establishment of criteria for control samples that are used to accept or reject runs and imprecision limits for individual samples), and then in-study validation continues to verify it. Critical changes to methods often require additional validation (partial or full), sometimes leading to the revision of the system suitability criteria.

Minimum Required Dilution

During assay development the minimum required dilution (MRD) can be defined as the dilution level of the ADA negative sample that results in the highest signal-to-variability ratio (or Z' factor).

The ability to dilute such samples also should be assessed to ensure that the chosen MRD is adequately distal to any prozone (hook) effects that may have been observed. Although they are rare, some unusual prozone effects may require the test method to include more than one dilution of a test sample to minimize false negative data.

The MRD should be evaluated during the assay development/design phase, i.e., before analysts initiate the validation experiments, so analysts do not need to repeat the evaluation during validation. It can be established using 10 individual drug-naïve ADA negative samples, each tested in 2-fold serial dilutions (e.g., a range of 1:5 to 1:80). The MRD is sometimes defined as the dilution level that results in the highest signal-to-background ratio when typically the background is the dilution matrix. However, this definition ignores the variability in the signal. Therefore it is preferable to define the signal-to-background value and include variability.

One way of doing this is to use a Z' factor that includes both the intensity of the assay readout and its variability at different dilutions (see the *Appendix* for more information). The Z' factor for each dilution level is obtained from the formula $[(\text{mean}(S) - 3 \text{ SD}(S)) - [\text{mean}(B) + 3 \text{ SD}(B)] / [\text{mean}(S) - \text{mean}(B)]$, where S is the assay signal of the diluted sample and B is the background signal. Thus, the MRD is the dilution that results in a desired value for the Z' factor and signal-to-background ratio. This metric is widely used for high-throughput screening assays to ensure adequate confidence in the ability to differentiate between truly

active versus inactive compounds. An inappropriately large MRD can compromise the sensitivity of an assay.

Pre-Study Validation

Pre-study validation establishes the following:

1. Assay cut-points
2. System suitability criteria
3. Relative sensitivity
4. Specificity
5. Selectivity/interference
6. Precision
7. Robustness
8. Reproducibility
9. Stability

Assay Cut-Points

Because of the quasi-quantitative nature of ADA detection methods, the use of a decision threshold or cut-point becomes necessary to discriminate between ADA-positive and -negative samples. Because the screening assay and specificity confirmation assay produce different types of results, separate cut-points are necessary. In some instances, a different cut-point also may be necessary for evaluating titers of confirmed positive samples from the titration assay. Some key points in the evaluation process are summarized briefly below (more information is available in the *Appendix*).

Samples for cut-point evaluation: Samples from an appropriate population should be used for the development of assay cut-points. In some cases it may not be practical or feasible to obtain matrix samples from a population that has a target disease before initiating pre-study validation experiments. Consequently, samples from healthy drug-naïve subjects are used commonly to establish the initial cut-points. This approach is preferred for a conventional Phase 1 study with normal volunteers. When the clinical program progresses beyond Phase 1 and samples from the target disease population become available, it is more appropriate to re-evaluate cut-point data for the target population. If the distribution of assay responses with respect to both the mean and variability are comparable between the target population and the normal volunteers, then the same cut-point can be used. If not, target disease-specific cut-points are more appropriate, and fixed or floating cut-points computed from the data obtained from the baseline samples from a clinical trial can be considered.

Screening cut-points: The screening assay cut-point is a signal in the screening assay that identifies a sample that is likely to contain ADA (termed a *screen positive* or *potential positive* sample) versus an ADA-negative sample. A screening assay cut-point is established during pre-study validation based on a systematic and statistically rigorous analysis of assay responses from a panel of individual samples that are considered to be representative of a drug-naïve target patient population.

To determine the screening method cut-points for clinical assays, analysts should use samples from at least 50 drug-naïve individuals for a robust evaluation. If additional indications are targeted, analysts should test at least 20 drug-naïve individuals per indication. If the variability is significantly different from the original indication, then additional drug-naïve individuals may need to be tested. If not, then the original cut-point can be applied to the additional indication. For nonclinical assays a total of at least 25 drug-naïve individuals should suffice. To ensure this cut-point is robust, at least two analysts should perform this experiment over three days in at least two different plate layouts. A balanced experimental design and plate layouts will help avoid potential confounding between analysts, subject samples, run dates, etc. For clinical ADA assays, if multiple disease-state populations are being tested they should be distributed evenly across the plates to ensure they are properly bal-

anced across plates and runs. Statistical outliers of the sample results should be examined and eliminated, e.g., using outlier box plots defined in terms of quartiles and interquartile range. In addition, confirmed reactive samples (e.g., via immunodepletion) can be excluded as well.

Three types of screening cut-points can be calculated for application during the study phase—fixed, floating, and dynamic—and one of these should be appropriately chosen for study phase bioanalysis.

Fixed cut-point—A fixed cut-point is a cut-point that is determined in pre-study validation and subsequently is used for the in-study phase. The fixed cut-point is used for analyses of test samples until there is a need to revalidate or change the cut-point (e.g., because of a critical change in the assay, assay transfer to another laboratory, upgraded instruments, etc.). The cut-point value can be fixed within a given study, for a target population, or across studies and multiple target populations. In order to use this approach, one should statistically demonstrate similar means and variances across runs during pre-study validation. A fixed cut-point can be determined based on the mean + 1.645 SD (standard deviation), which represents the 95th percentile of the population under normal distribution (and therefore is expected to identify approximately 5% of the samples as false positives). The standard deviation should include different sources of variation such as the intra-run, inter-run, inter-analyst, and inter-subject variability. If the data are not normally distributed, appropriate transformations (typically log transformations) can be used. If transformation doesn't help, usually it is acceptable to determine the nonparametric 95th percentile. However, in preclinical trials it may be considered adequate to use a cut-point at the 99th or 99.9th percentile because immunogenicity of a protein normally results in high antibody titers. Alternatively, even if the validation data suggest similar means and variances across runs, to account for possible deviations between assay runs during the in-study bioanalysis phase, it would be safer to apply a floating cut-point.

Floating cut-point—A floating cut-point is a cut-point calculated by applying an additive or multiplicative normalization factor, determined from the pre-study validation data, to the biological background obtained during the in-study phase (see Appendix G of Shanker et al., 2008, in the Appendix for details). The biological background may be represented by the negative control (pool of matrix from subjects that are negative for ADA), the assay diluent, or the predose subject sample (subject-specific cut-point). The method for determining floating cut-point uses the variation estimate from the pre-study validation that includes different sources of variation such as the intra-run, inter-run, inter-analyst, and inter-subject variability. Such a cut-point is recommended when the means of drug-naïve samples are not similar but the variances are similar across runs. When a negative control is used for normalization, analysts also should ensure that the negative control results represent the drug-naïve matrix sample results of the target population. This is accomplished by demonstrating that the signal of the negative control trends directionally with the signal of the individual samples. Alternatively, the use of assay diluent for normalization or pretreatment subject ("baseline") sample results may be more appropriate. However, a pre- versus post-dose ratio might be a better solution.

Dynamic cut-point—A dynamic cut-point is a cut-point that changes between the plates in a run, between runs in a study, or between studies, and it does not apply the variation estimates from pre-study validation. The latter characteristic differentiates it from a floating cut-point. This approach is necessary only where means and variances significantly differ between runs. Because this approach entails testing of several individual drug-naïve samples for the evaluation of a run-specific cut-point, it consumes a large portion of the plates from each in-study run and therefore is not practically feasible, especially when analysts use 96-well plates instead of 384-well plates. Differences in variability

between assay runs sometimes can be resolved by further optimization of some key steps in the assay protocol or by resolving some analytical issues. In some cases, the differences in variability can be attributed to different analysts or instruments, and use of an analyst-specific or instrument-specific floating cut-point may resolve this issue. If further optimization does not resolve the situation or if the causes are not clear, another practical alternative may be to pool the variability across all runs and use this pooled variance for floating cut-point evaluation during the in-study phase.

Specificity confirmation method cut-point: Because of the conservative approach of incorporating a 5% false-positive rate into the computation of the screening cut-point, the elimination of false-positive samples via confirmation of drug-specific binding is an important component of ADA bioanalysis. It is also important to understand the level, if any, of the drug itself within the sample.

The amount of change in assay signal that differentiates drug-specific binding from nonspecific binding is referred to as the *specificity cut-point*. The specificity cut-point should be determined by an objective approach in the context of assay variability near the low positive range of the assay. To determine the specificity cut-point, drug-naïve negative samples from at least 25 individuals should be evaluated (however, more are commonly used when available), with and without drug preincubation. Ideally these samples should be the same as those tested during the screening cut-point evaluation, and the unspiked and spiked counterparts of the individual subject samples should be tested together in the same plates.

The mean percent change from the unspiked sample (inhibition) and SD are calculated. The mean inhibition plus 3.09 SD (if a 0.1% false positive rate is desired) represents the specificity cut-point. As in determination of the screening cut-point, specifically reactive samples after preincubation with drug (i.e., those that contain pre-existing antibodies) and statistical outliers should be eliminated in order to make the specificity cut-point more conservative. The analytical process outlined above for the screening cut-point applies for the evaluation of the specificity cut-point as well.

Alternative approaches such as the use of *mock low positive* samples in which the individual drug-naïve samples are spiked with a low concentration of a positive control sometimes is considered for this cut-point evaluation. However this method is subjective and is not recommended because it depends on the concentration of the positive control and the unique affinity/avidity of the positive control that may or may not represent true positive patient samples. Additional sources of information regarding the relative statistical merits of these approaches and methods for verifying the assumptions are listed in the Appendix.

Titration method cut-point: The titration method cut-point is a test result value below which further serial dilution of an ADA-positive sample produces negative assay results. Typically, the screening assay cut-point is used as the titration cut-point, but the validation of a separate titration method cut-point can become necessary when the signal from the assay diluent or matrix causes higher results than the screening assay cut-point (because of a blocking effect of serum) or if samples at a dilution higher than the MRD do not generate consistently negative results, i.e., when the screening cut-point falls on the lower plateau of the positive-control dilution curve. In such instances, the same data generated during a screening cut-point experiment can be used to define the titration cut-point using a 0.1% false positive rate threshold criterion (i.e., Mean + 3.09 SD). During bioanalysis, confirmed positive patient samples that fall between the screening cut-point and titration cut-point can be assigned a titer value equal to that of the MRD.

Cross-reactivity method cut-point: If applicable, ADA-positive samples that are confirmed to be specific to the drug can be further characterized for cross-reactivity to other related antigens. Like the specificity confirmation assay, a cross-reactivity test method may require a preincuba-

tion step with and without the related antigen. Cross-reactivity to the antigen is confirmed when the percent inhibition of signal in the presence of the antigen is greater than or equal to the cross-reactivity method cut-point. The methods for determining the cross-reactivity method cut-point are similar to those for the specificity method cut-point, although it also may be acceptable to apply the drug specificity confirmation cut-point.

Defining System Suitability

Assay controls: ADA-positive controls can comprise polyclonal or monoclonal anti-idiotypic antibodies. They should be affinity purified and quantitated to enable assay validation. Each run (or plate) should include at least a low level of positive control (*low positive control*) and a negative control, but the inclusion of a higher level control (*high positive control*) also can be useful in monitoring method performance. Tracking all of these controls over time can help ensure that the method is performing suitably. A low positive control helps ensure that the assay remains as sensitive during study phase bioanalysis as during the pre-study validation.

On the one hand, the low positive control should produce a response that can be seen reproducibly above the cut-point, but sometimes it may result in a signal that is below the cut-point (thereby failing or invalidating the assay). On the other hand, choosing an unreasonably high concentration for a low positive control may produce an assay signal that is substantially above the cut-point, which is inappropriate. To provide objectivity to the selection of a low positive control concentration, it is useful to think in terms of assay rejection rates, i.e., the percentage of assays (plates) that fail because the low positive control produces a result below the cut-point. As an example and in order to understand if the low positive control is sufficiently low, a 1% rejection rate may be a reasonable target for a low positive control. This is calculated as $\text{mean} + t_{0.01, df} \times \text{SD}$, where mean and SD are determined using the data from the sensitivity experiment or related assay development data, and $t_{0.01, df}$ is the critical value determined from the *t*-distribution corresponding to a 1% false positive rate and *df* is the degrees of freedom that depends on the number of samples and runs used in the calculation. This theoretically implies that about 99% of the data from the low positive controls will be at or above the cut-point.

An optional high positive control can be useful for methods that are prone to hook effects, tracking assay performance, reagent qualifications, and troubleshooting. The concentration of the high positive control should be chosen from the upper end of the linear range of the dilution curve, usually just below the upper plateau of the curve.

System suitability criteria: System suitability criteria using assay controls help ensure that an analytical procedure remains valid for use. Acceptance ranges (system suitability criteria) for quality controls should be established by statistical evaluation of the experimental data acquired during assay validation.

When the floating cut-point approach is deemed necessary and is used for the screening cut-point evaluation, the system suitability criteria or limits can be defined for the ratio of the low positive control to the negative control and for the ratio of the high positive control to the low positive control or a negative control instead of defining limits separately for each positive control. It is also useful to apply acceptance criteria for intra-assay precision (variability of signals of replicates in an assay) for the in-study phase. Although data from assays that fail acceptance criteria during the in-study phase should be rejected, setting criteria for passing or failing assays in pre-study validation experiments should be avoided because these potentially can lead to the exclusion of some validation data, resulting in an inaccurate estimate of analytical error. All assays during pre-study validation should be included, and the only exceptions should

be those rejected for an assignable cause (e.g., technical error).

Relative Sensitivity

No ADA-positive control can be expected to represent the spectrum of humoral immune responses observed in individuals treated with study compounds. The sensitivity of ADA assays is highly dependent on the nature of the positive control reagent(s) so that high-affinity positive controls often produce better sensitivity values than lower affinity positive controls in the same assay. Analysts should consider this when they choose controls, as well as when they estimate assay sensitivity. Moreover, because the drug itself can interfere with ADA detection, the sensitivity of ADA detection becomes progressively worse in the presence of increasing concentrations of drug within the sample. Despite these caveats, the determination of assay sensitivity is valuable when analysts choose an optimal ADA detection method or platform, a low positive control for validation, or assess the suitability of an assay. The assessment of assay sensitivity in the presence of an interfering drug (drug tolerance) is critical for understanding the suitability of the method for detecting ADA in dosed patients. ADA assay sensitivity should be defined not as a single value, but as a set of at least two values: (1) the concentration of positive-control ADA detected within undiluted matrix in the absence of any drug and (2) the concentration of positive-control ADA detected within undiluted matrix in the presence of drug levels expected at the time points when samples for ADA analysis are taken. Assays should, in general, demonstrate a sensitivity of at least 500 ng/mL for methods applied to clinical studies (or 1000 ng/mL for nonclinical studies) to show suitability for intended purpose—that is, for the detection of clinically meaningful ADA, although assay sensitivity should be justified on a case-by-case basis. It is not useful to express sensitivity in terms of antiserum titers, and thus sensitivity should be assessed using monoclonal antibody or affinity-purified polyclonal preparations. Analysts can evaluate sensitivity by means of two assay runs performed by two independent operators (when feasible) for a total of at least three runs.

To assess sensitivity in the absence of a drug, analysts should prepare mock samples with known concentrations of ADA that are serially diluted (usually 2- to 3-fold serial dilutions) in matrix pooled from drug-naïve individuals and evaluated according to the screening method until the assay results of the dilutions in matrix are below the screening assay cut-point. The lowest concentration of ADA that is consistently found (for example, using a 95% upper confidence limit based on the number of runs or operators) above the screening assay cut-point is determined to be the sensitivity of the assay. Alternatively, it can be the lowest concentration of ADA that is found to be above the screening assay cut-point in all runs by all operators or in 19 of 20 runs (see the *Appendix* for more information).

To assess sensitivity in the presence of a drug, two alternative experimental approaches could be considered: (1) titrate the drug into undiluted matrix containing set concentrations of a positive-control ADA (e.g., 250, 500, or 750 ng/mL). Report the highest concentration of the drug at which ADA remains detectable. (2) Alternatively, because immunogenicity samples often are taken at drug trough time points, prior knowledge of the anticipated trough drug concentration range could be used to determine the assay sensitivity in the presence of the expected concentrations of the drug.

Specificity

Specificity refers to the ability of a method to detect ADA that specifically binds the drug molecule, its domains, or components. The assay is developed and optimized based on the ability of the positive-control ADA to specifically bind

the drug. During validation, results of the specificity confirmation assay support assay specificity.

Selectivity and Interference

The selectivity of an ADA assay is its ability to identify a positive control in biological matrix samples that may contain potential interfering substances and is an important concern for ADA detection assays. Such matrix effects typically arise from nonspecific binding interactions between a matrix-based factor and the ADA or from specific binding of unknown factors. During validation, analysts assess the selectivity of the ADA assay by looking at the recovery of analyte (represented by a positive control sample) from matrix samples that contain the potential interferent(s). One caveat here is that the selectivity of an ADA assay, as assessed using the positive control, may not reflect the selectivity of the assay when it is used with actual nonclinical or clinical samples.

Interference is the property of a factor (most commonly the drug itself and its target, if soluble) to affect assay results positively or negatively. It should be evaluated using a low positive ADA test sample that is spiked into a sample matrix from drug-naïve patients. Each potential interfering factor should be tested at a physiologically or pharmacologically relevant range of concentrations. The highest concentration of the interfering factor that does not alter the classification of the test sample (e.g., an ADA sample that remains positive relative to the screening assay cut-point) is defined as the tolerance of the assay to that interfering factor. For therapeutics that have a long terminal half-life, the main interferent in an ADA assay is the drug itself. As discussed previously, the drug tolerance of an assay should be interpreted as the sensitivity of the method in the presence of interfering drug.

Other endogenous interferents include oligomeric drug targets, or the target's soluble receptor may interfere with ADA detection. In addition, certain sample pretreatments performed to reduce drug interference can release drug target from drug-target complexes, leading to subsequent interference problems. Hence, analysts should carefully evaluate pretreatment steps such as acid dissociation during assay development to mitigate the risk of inaccurate data.

Precision

Precision is a measure of the variability in a series of measurements for the same material run in a method. The acceptance criteria for the precision of ADA assays should be within the range commonly expected for immunoassays. These criteria also should be appropriate for the assay platform and should be fit for purpose. During assay validation, precision should be determined in experiments that are run at the level of intended use during the study phase (e.g., number of plates, samples per plate, etc.).

The acceptance criteria for precision should be within the range commonly expected for immunoassays. These criteria also should be appropriate for the platform used, guided by assay development data and experience with the technology platform and assay method. Additional information is found in the *Appendix*.

Screening and confirmatory method precision: For ADA screening assays with numeric readouts (as opposed to categorical yes/no readouts), assay precision can be determined using data from at least six independent assay runs of the assay positive controls (low positive and high positive controls). Typically, estimates of intra-assay precision (interreplicate variability, also called intra-assay repeatability) and interassay precision (also called interassay repeatability, or intermediate, total, or overall precision) are reported as percent coefficient of variation (%CV).

Intra-assay precision (repeatability) is the variability of assay results when the same material is tested multiple times

within the same run. Interassay precision (also termed intermediate or total precision) is the variability of assay results when the same sample is tested in separate runs, over separate days, and by multiple operators (or only one operator if the study phase bioanalysis is intended to be performed by only one operator). These are expressed as %CV of ADA signals. Data from the replicates of negative and positive controls from each of all the runs tested during the pre-study validation phase are pooled and analyzed within the framework of random-effects ANOVA, resulting in estimates of intra-assay %CV and interassay %CV. Analysts should consider positional effects by varying sample position on microtiter plates because these effects (e.g., edge effects) can influence the assay precision. One should use the same number of test and control sample replicates during validation as are used in the assay during routine use.

Similarly, intra- and inter-assay precision estimates for the confirmatory assay can be derived using the percent inhibition data of the spiked versus unspiked low positive control samples from multiple assay runs (at least six) in the pre-study validation.

Titration assay precision: In order to determine the precision of a titer, two or more analysts should assay serial two-fold dilutions of five or more mock high positive control samples in at least six runs. Mock high positive control samples can be obtained by spiking individual negative sera from the target population with a high positive sample. The titer then is determined by interpolation of each of the dilution curves, and the overall mean and SD are calculated. Then intra- and inter-assay precision (%CV) can be determined.

A recommended but more rigorous approach is to use these data to define a minimum significant ratio (MSR): $MSR = 10^{t \cdot \sqrt{\ln(2)} \cdot SD}$, where SD is the overall standard deviation (intra-run plus the interrune variation) of the titers in common (base 10) log scale, and t is the threshold from Student's t -distribution with $n - 1$ degrees of freedom (n = number of runs). The calculated MSR reflects the smallest fold-change in the titer values that can be considered as statistically significant ($P < 0.05$)—i.e., if $MSR = 5$, then titers that are different by more than five-fold can be considered significant. In addition to serving as an indicator of the level of variability in the titers of the positive control, this MSR evaluation also can be an approximate criterion for comparing samples with confirmed pre-existing antibodies in baseline versus posttreatment samples in order to assess treatment-induced immunogenicity. The MSR applies only if the titer is interpolated and does not apply to endpoint titers.

Robustness

Robustness is an indication of the reliability of an assay. It is assessed by the capacity of the assay to remain unaffected by small but deliberate variations in method performance that would be expected under relevant, real-life changes in standard laboratory situations. The choice of robustness variables to test during validation should be based on the knowledge of the assay and its associated risks. Some common variables are microtiter plate lots, incubation times, temperature, and reagent lot and concentrations. Study samples or positive control samples can be used to test assay robustness. The use of acceptance criteria for system suitability controls during robustness validation (computed from the assay development and optimization data or validated system suitability control acceptance criteria) is recommended. Continuous monitoring of an assay during validation and beyond with strict records of key assay parameters (e.g., incubation times, pipetted volumes of critical reagents, operators, etc.) may help identify some of the robustness factor interactions if sufficient data are accumulated.

Reproducibility

Assay reproducibility according to USP general chapter *Validation of Compendial Procedures* (1225) and ICH Q2(R1) *Validation of Analytical Procedures: Text and Methodology* is the reliability of a method when performed in two or more laboratories. In the context of method transfers and interlaboratory method validity demonstrations, assay reproducibility is the same as a cross-validation.

Reproducibility is applicable only if an assay will be run by two or more independent laboratories during in-study phase bioanalysis. Reproducibility is an assessment of the transferability of an assay, i.e., the validity of testing samples in two or more laboratories and the comparability of data produced by them. Reproducibility assessments do not consider routine changes in an assay such as interequipment or interanalyst imprecision. Such contributors to variability (often referred to as intermediate precision factors) are part of the reproducibility variability.

Study phase acceptance criteria for system suitability controls are established in the originator laboratory (see below) during the original assay validation process. The performance of these controls can be compared across multiple laboratories. When only a single laboratory performs the ADA assay, however, reproducibility need not be validated until the method will be transferred to another laboratory.

Stability

It is useful to understand the optimal storage conditions for assay samples, controls, materials, and reagents, and they should be investigated as part of assay optimization before validation. Later, during assay validation, stability studies should evaluate assay performance following intended storage conditions. Ideally, stability testing conditions should mimic the expected sample, material, and reagent handling conditions, storage temperature(s), and varying lengths of storage time.

Material and reagent stability: ADA assays are stability indicating with respect to the applicable materials and reagents, and thus separate tests for reagent stability usually are not required for assay validation. During study phase bioanalysis, assay materials and reagents are presumed to be stable if the system suitability controls meet validated acceptance criteria. However, analysts should validate the stability of plates that have been prepared in advance (e.g., coated with capture antibody and blocked) and stored.

Sample handling and stability: ADA samples typically are collected in a serum or plasma matrix. For samples stored at or below -20°C , the stability of ADA are universally accepted, so this sample storage condition may not require validation. It is generally accepted that an ADA sample in serum or plasma will be stable after three freeze–thaw cycles and up to 2 years when stored at -70°C .

Documentation of Pre-Study Validation

Typically three types of assay-specific documents are created during pre-study validation: an assay validation plan or protocol, an assay method description, and an assay validation report.

An assay validation plan or protocol is recommended before analysts initiate pre-study validation experiments. This document should state the intended purpose of the method, a detailed description of the immunoassay and reagents or materials, a summary of the performance characteristics that will be validated, and a priori acceptance criteria for precision, robustness, stability, and, when appropriate, reproducibility. Some experimental detail and data-handling procedures should be presented in the validation plan because these details provide a clear guidance to

the validation analysts and ensure better control over the resulting data.

A method description typically is established after pre-study validation but before the study. This provides a detailed description of the reagents, controls, and equipment needed to run the assay, together with a step-by-step operating procedure and information about processes for data reduction and interpretation. The point at which such a description becomes a Standard Operating Procedure (SOP) is specific to each manufacturer's quality system.

When validation is completed, manufacturers generally conduct a technical peer review of validation data, followed by a validation data audit. An assay validation report is created after the validation work is completed. This documents all of the study validation data, together with information about the methods and batches of reagents that were used. An audited report is approved by management and then is archived.

In-Study Validation

In-study validation (monitoring the maintenance of system suitability) and revalidation are critical components of any bioanalytical method. Hence, the validation of a method actually does not end until the method is retired from analytical use.

For in-study performance of quantitative bioanalytical methods, acceptance criteria for precision and accuracy generally are required. Because accuracy is *not* applicable for ADA methods, monitoring the performance of quality control samples reassures analysts that the assay system is suitable for its intended use, i.e., that the assay remains valid and is performing as well as it did during pre-study validation.

The use of a low positive control ensures the assay remains sensitive. Generally during study sample analysis the intra-assay (interreplicate) precision of the results of positive controls, as well as test samples (with assay signal at or higher than the screening cut-point), are controlled using system suitability acceptance criteria to ensure that meaningful data are consistently obtained. Results below the cut-point, however, may not be required to meet CV limit criteria.

LIFE CYCLE MANAGEMENT

Management of the performance of immunogenicity assays from initial clinical development through subsequent product life cycle requires a comprehensive understanding of the strengths, weaknesses, and capabilities of the method format, as well as of the critical assay reagents and assay performance characteristics. In addition, a well-defined plan for critical reagent production, characterization and qualification, qualification of suppliers of critical reagents, and characterization and qualification parameters for reagents produced in-house (aggregate level and labeling efficiency) help manage the risk of maintaining the assay and transferring the method to other laboratories.

When there are changes in critical method components, equipment, or the population that is studied with a particular ADA assay, an assay revalidation may be required. The revalidation may cover some or all validation characteristics (i.e., it may be a partial or whole assay revalidation). Use of lots or batches of assay critical reagents that are different from those used in pre-study validation do not require assay revalidation, but they must be supported by appropriate experimental qualification data for the new reagent to ensure maintenance of system suitability.

Another critical aspect of life cycle management is the development of a strategy to bridge clinical data between an existing and an improved assay format. Such changes typically occur in a product's life cycle because of postmarketing commitments or other needs. To facilitate

comparison and cross-validation of the existing method to the revised versions, analysts should retain sufficient aliquots of the original lots of critical assay reagents. In addition, archiving of analyte-spiked samples as well as blinded patient samples is useful to bridge between reagent lots and methods in order to minimize drift in assay performance. Analysts should develop a written plan outlining the sort of changes to the existing assay or critical reagents that will warrant an assay qualification versus a cross-validation or full validation. A quality management document should include details such as the number of assays that must be performed, the number of analysts that will be used, required training for analysts, acceptance criteria to demonstrate equivalence between existing and revised methods, data analysis, and reporting method. This information demonstrates the robustness and consistency of the assay following changes. Quality controls that ensure assay equivalence include %CV, tolerance limits, EC₅₀ values of slope, titer level, and signal-to-noise ratio. One approach commonly used to demonstrate equivalence of two immunogenicity methods is the demonstration of ≥90% concordance in archived sample results between the existing and revised methods.

Analysts should use archived samples with a range of positive values as well as an appropriate number of negatives to verify that a new assay segregates samples into positive and negative categories in the same manner as an existing one.

Another important consideration for life cycle management of critical assay reagents is the monitoring of long-term reagent stability under different storage conditions. A detailed stability testing plan includes storage temperatures (4°C, –20°C, and –70°C), aliquot volume, freeze–thaw cycles, and acceptable performance characteristics for assay qualification, and results should be documented. In this context, it may be prudent to archive patient samples to demonstrate the long-term stability of the polyclonal ADA response in actual patient samples.

APPENDIX: ADDITIONAL SOURCES OF INFORMATION

Nonclinical Immunogenicity Testing

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<1118> MONITORING DEVICES— TIME, TEMPERATURE, AND HUMIDITY

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■INTRODUCTION

This chapter provides background information about the science and technology of temperature and humidity monitoring over time. It describes the available technologies and performance characteristics, and provides recommendations for qualifying performance. The shelf life of a drug product is a function of the temperature and humidity conditions during storage and transportation, as well as the drug product's chemical and physical properties. For this reason, the ability to monitor those conditions is important in the shipping and storage of temperature- and humidity-sensitive drug products. This chapter focuses strictly on supply chain temperature- and humidity-monitoring devices, both electronic and chemical.

The storage and distribution temperatures may be different if justified by appropriate stability studies and as indicated in the labeling. The effects of humidity are typically observed over longer time periods of exposure than are temperature effects due to the barrier to moisture ingress presented by the primary and secondary drug product packaging.

The devices described in this chapter are those most commonly used to monitor the controlled storage and established distribution of drug products following Good Distribution Practices (GDP).¹ The chapter does not address measurement of temperature at extremes, which are temperatures above those that drugs are reasonably expected to experience in the supply chain. The types of devices described are already used in the worldwide distribution of pharmaceuticals and by other similar industries that require temperature control in distribution (for example, the perishable food, blood component, and medical device industries). Devices also may be attached to individual items for the end user (for example, vaccine vials in the World Health Organization (WHO)/UNICEF global immunization program).² Appropriate recycling practices should be followed for all devices as required by local regulations.

TEMPERATURE-MEASUREMENT DEVICES

Alcohol or Mercury Thermometers

These devices are based on the change in volume of a liquid as a function of temperature. Both types of thermometers can be designed to indicate the maximum and minimum temperatures (see *Thermometers* <21> for more information). Historically, these types of thermometers are used in a laboratory setting or in a pharmacy, rather than during supply chain monitoring. Alcohol thermometers can have a precision as good as 0.01°, but they must be quite large to

measure temperatures in ranges of more than a few degrees.

Mercury thermometers are typically used in the ranges from 0° to 50° with a precision of about 0.1°. Some local regulations apply to mercury-based thermometers, and many states and local agencies have legislated or developed collection or exchange programs for mercury-containing devices. The U.S. Environmental Protection Agency also issues regulations requiring industry to reduce mercury releases to air and water, and to properly treat and dispose of mercury wastes to avoid potential health hazards.³ Globally, Health Care Without Harm and WHO are co-leading a Health Care Initiative Products Partnership to reduce demand for mercury-containing devices by at least 70% by 2017 and to shift production to accurate, affordable, and safer nonmercury alternatives.⁴

Both alcohol and mercury thermometers are more fragile than other temperature-measuring devices described in this chapter.

Infrared Devices

This device is used for measuring the infrared (IR) radiant heat from the article whose temperature is being determined, and the IR reading varies as a function of the object's temperature. The advantage of this type of device is that the article may be at some distance from the IR sensor. IR devices may give inaccurate higher or lower temperature readings because of the surface characteristics of packages (e.g., black vs. white surfaces), and they also have the potential for operator error because of incorrect use of the IR reader (improper angle).

Resistance Temperature Detectors

The resistance temperature detector (RTD) is based on the change in electrical resistance of a material as a function of temperature. The precision and accuracy of an RTD depend on the quality of the electronics used to measure the resistance. Although RTDs are among the most stable and accurate temperature sensors, their accuracy may change with the age and temperature of the device because its electronic components are affected by age and use. Although all temperature-measurement devices should be placed on an appropriate calibration program as recommended by the manufacturer or user of the device, this calibration is particularly important for RTDs.

Solid-State Devices

Solid-state devices are based on the effect of temperature on either an integrated circuit (see *Thermistors*) or a micromechanical or microelectrical system. These devices are commonly referred to as data loggers, and can attain high precision and have the advantage of producing a digital output.

Thermistors

A thermistor is a semiconductor device whose resistance varies with temperature. Thermistors are able to detect very small changes in temperature and are accurate over a broad range of temperatures.

Thermocouples

Thermocouples are based on the change in the junction potential of two dissimilar metals as a function of temperature. Many metal pairs can be used, and each pair provides a unique range, accuracy, and precision. Precision and accu-

¹ PDA Technical Report 52 (TR 52) Guidance for Good Distribution Practices (GDPs) For the Pharmaceutical Supply Chain.

² World Health Organization (WHO)-UNICEF Policy Statement on the Implementation of Vaccine Vial Monitors: The Role of Vaccine Vial Monitors in Improving Access to Immunization, http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.04_eng.pdf.

³ <http://www.epa.gov/mercury/>.

⁴ <http://www.noharm.org/>.

racy depend on the quality of the electronics used to measure the voltage across both metals and the type of temperature reference used.

Thermomechanical Devices

Thermomechanical devices are based on the change in length of a solid material as a function of temperature. An example of such a device is a mechanical spring, which expands or contracts as a function of temperature, thus opening and closing an electrical circuit or moving a chart pen. Typical examples are chart recorders used in cold rooms.

ELECTRONIC TIME–TEMPERATURE HISTORY RECORDERS

These recorders use one of the electronic temperature-measurement technologies described above and create a record of the temperature history experienced.

Electronic Time–Temperature Indicators

Electronic time–temperature indicators (TTIs) can be designed to alarm after a cold excursion, heat excursion, or after multiple temperature excursions and can provide a visual alarm by a colored light or LCD. The alarm(s) are generally programmable and can display conditions such as date, time, temperature, and duration of the alarm. A certificate of calibration is issued for individual units or lots. Multiple-use devices should have a calibration schedule, but single-use devices can rely on manufacturers' certificates of calibration.

Electronic Temperature-Data Loggers

Electronic temperature-data loggers are recorders that monitor the temperature at programmable intervals and save the temperature history to a peripheral system, such as a personal computer. In addition, data loggers can record humidity using sensors described below. Electronic recorders monitor and save temperature values representative of the cumulative temperature history over a period of time and therefore have the advantage of being able to calculate the mean kinetic temperature (MKT)⁵ based on the measurements. Data loggers equipped with transmitting devices (hardwired or radio transmission) can be used to monitor the temperature and humidity of a product while in transit and can download the recorded data when the data loggers arrive at a destination. Data loggers are increasingly required by worldwide ministries of health as part of a standard quality system for GDPs. Based on their communication capabilities, data loggers can be grouped into several different categories.

Radio-Frequency Data Loggers

In addition to data loggers that require a hardwired connection to a base unit or a computer, in recent years companies have adapted wireless (radio-frequency or RF-enabled) temperature and humidity recorders. The effects of radio-frequency identification (RFID) use on biologics have been studied on a variety of blood, blood components, monoclonal antibodies, and vaccines, and have demonstrated no effect.⁶ These loggers are integrated with chips capable of wireless RF communications that constitute the

RFID sensor tags. The RFID chip inside the tag can be either active, which requires battery power for operation, or passive, which requires a nonzero RF field created by the RFID interrogator host unit (commonly called the reader) in the vicinity of the tag. RFID-enabled sensor tags (temperature and/or humidity) have the added capability of conveying recorded temperature history wirelessly to a host computer or database for seamless downstream processing. Multiple passive and active standards exist to control the communication between the tag and the host unit, including ISO-18000-6C,⁷ ISO-18000-7,⁸ ZigBee,⁹ IEEE 802.11,¹⁰ and many proprietary standards.

When choosing between active and passive technologies, one needs to know that active technologies typically have extended communication range and memory capabilities at the expense of a higher price. Currently, reading ranges extend to 100 m and with repeaters longer distances can be achieved. Whether the communications circuitry is passive or active, these RF loggers still are electronic temperature recorders, which means their sensor circuitry uses external power from batteries or other sources.

A completely passive wireless RFID tag with an antenna capable of functioning as a sensor has been developed. The tag uses resonant antenna structures of RFID tags that are coated with specific sensor films. The passive wireless RFID tags act like analog sensors that, when interrogated by a wireless reader, show the instantaneous temperature. The film changes the antenna's reflection characteristics based on the monitored environmental variable (such as temperature and/or humidity), which then is decoded by the reader. The sensor film can be designed to work with different variables such as temperature, humidity, and various gas and chemical vapors. Although they lack some of the memory functionality included in electronic recorders, passive wireless sensors are relatively cost effective compared to data loggers and can be considered for item-level applications.

CHEMICAL TEMPERATURE INDICATORS

Chemical temperature indicators are relatively cost effective compared to electronic data loggers and can be considered for item-level applications. There are two basic types of chemical temperature indicators: 1) a threshold indicator that responds at a specific temperature and 2) a TTI that responds to cumulative heat exposure.

Chemical Temperature Threshold Indicators

These indicators, sometimes referred to as critical temperature indicators, are based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, polymers, and lacquers that change phase, and thereby their appearance, as a function of temperature. Chemical temperature threshold indicators are reversible or irreversible and are suitable for high or low temperatures. Temperature threshold indicators do not include any specified time delay to show a response and typically are single-use devices. These indicators provide a signal only when exposed to temperatures higher than (ascending indicator) or lower than (descending indicator) a predetermined threshold temperature.

Ascending-Temperature Threshold Indicators—Ascending-temperature threshold indicators are supplied as self-adhesive labels or cards and are normally composed of a heat-fusible compound that melts at the critical tempera-

⁵ The Use of Mean Kinetic Temperature (MKT) in the Handling, Storage, and Distribution of Temperature Sensitive Molecules. R. H. SeEVERS, J. Hofer, P. Haber, D. A. Ulrich, R. Bishara. *Pharmaceutical Outsourcing*, May/June, 30–37, 2009.

⁶ Effects of Radio Frequency Identification-Related Radiation on In Vitro Biologics. I. Uysal, C. Hohberger, R. S. Rasmussen, D. A. Ulrich, J. P. Emond, A. Gutierrez. *PDA Journal of Pharmaceutical Science and Technology*, Vol. 66(4), July/Aug, 333–345, 2012.

⁷ ISO/IEC 18000-6:2010—ISO/IEC 18000-6:2010—Information technology—Radio frequency identification for item management—Part 6: Parameters for air interface communications at 860 MHz to 960 MHz.

⁸ ISO/IEC 18000-7:2009—Information technology—Radio frequency identification for item management—Part 7: Parameters for active air interface communications at 433 MHz.

⁹ IEEE 802.15.4—Wireless Medium Access Control (MAC) and Physical Layer (PHY) Specifications for Low-Rate Wireless Personal Area Networks (LR-WPANs), 2003.

¹⁰ IEEE 802.11—Wireless Local Area Networks (LANs), 2007.

ture. Melting of the compound gives rise to a color change or color development. Other types are provided as inks, lacquers, pellets, or crayons. Ascending-temperature threshold indicators are available from 0° to more than 200° and as many as 10 temperatures on a single unit. Some ascending-temperature threshold indicators used to monitor frozen or refrigerated temperatures require an activation step (such as a pull tab or a reservoir that is ruptured by pressure).

Descending-Temperature Threshold Indicators—Descending-temperature threshold indicators show a response when exposed to temperatures below a threshold. These indicators do not include a specific time delay to show a response, and the response is typically caused by the time required for solidification of a liquid at the threshold temperature. Solidification of a liquid causes a visual change in the indicator. Examples include: 1) the expansion of the liquid to crack an ampule and release a colorant, 2) contraction of the liquid to mix components to develop color, or 3) aggregation of colloidal particles to change color.

Chemical Time–Temperature Indicators

These indicators, sometimes referred to as time–temperature integrators (TTIs), include systems in which a reaction rate or diffusion process is used to estimate a temperature equivalent integrated over time. Thus, TTIs provide a measure of accumulated heat rather than instantaneous temperature such as a spike or critical threshold (discussed above). The reactions generally are irreversible—once a color change, color development, or diffusion process has taken place, exposure to low temperatures will not restore the indicator to its original state, but lower temperatures (refrigeration) will slow the color change. The accuracy and precision of these indicators depend, to some extent, on human interpretation. Some versions of chemical indicators have been prepared in a bar code format and can be read with bar code readers. Other developments include reading a chemical indicator with an imaging device such as a camera in a smart phone.

TTIs do not directly reflect the status of the drugs to which they are attached. In actual practice, the characteristics for degradation of a particular drug are known from accelerated and real-time stability studies that follow internationally accepted guidelines such as PDA TR 53¹¹ to guide selection of a suitable TTI.¹² The activation energy of the TTI is not required to exactly match the activation energy of the degradation of the drug being monitored, and the latter, in fact, may not be known precisely. Therefore, the TTI should be chosen to provide an early warning if the drug is exposed to an excessive heat load before the expiration date.

An important characteristic of chemical TTIs is the precision with which the end point can be determined. For TTIs that change color, a reference color normally brackets the active portion of the TTI to show the end point color, which simplifies TTI interpretation. Accuracy can vary widely with the control and quality of the manufacturing process. Some TTIs are manufactured by procedures that comply with Quality System Regulations for Medical Devices. As discussed below in *Calibration of Temperature- and Humidity-Monitoring Devices*, it is not possible to calibrate any individual single-use device because the test is, by the nature of the TTI, necessarily destructive. This is analogous to any pharmaceutical product because each dose cannot be calibrated or validated, but validated processes should be used in the manufacturing process.

The two types of TTIs are partial-history indicators and full-history indicators. Partial-history TTIs provide a time- and

temperature-dependent response when the temperature exceeds a predetermined value. A partial-history indicator normally is composed of a dyed, heat-fusible compound that diffuses along a porous strip or wick when the temperature exceeds the melting point of the compound. The diffusion process of the compound down the wick is temperature dependent, and therefore the partial-history TTI provides a time and temperature response above the melting point of the compound. Migration of the compound down the wick stops when the indicator is moved to a lower temperature at which point the compound solidifies. These TTIs normally have one or more viewing windows to monitor the length the dyed compound has traveled along the wick. Some indicators are activated by removing a barrier film that separates the dyed compound from the wick or rupturing a reservoir that contains the dyed compound. Other indicators do not require activation and must be stored below the melting point of the compound before use. These partial-history TTIs can have durations (service life) anywhere from several hours to several years. Full-history TTIs provide a continuous response to temperature. They change color or physical appearance as a result of exposure to time, and the rate of change increases with temperature so they are sensitive to cumulative heat exposure. Full-history TTIs are responsive to MKT (Ref 1079) and typically are single use, irreversible, and disposable because once the color changes it will not revert to the original color.

Chemical–Physical Time–Temperature Indicators

This type of TTI is based on a temperature-dependent diffusion or chemical reaction process. It consists of a pressure-sensitive tape device that is composed of an indicator tape and an activator tape. In one example, the indicator tape contains a dye precursor dispersed in a polymer carrier. The activator is incorporated into an adhesive on the activator tape. Laminating the activator tape over the indicator tape causes activation. A color change or readable message occurs as the activator migrates into the indicator as a function of temperature and time. Other approaches to develop color changes include the use of a pH indicator or the etching of aluminum by the activator tape.

Chemical Polymerization–Based Time–Temperature Indicators

This type of TTI uses a solid-state polymerization process in which a color develops intensity as a function of time and temperature. The color evolution is caused by the polymerization of a colorless monomer to a highly colored polymer. These TTIs can be applied by a print process that permits direct integration into a product label or stand-alone label. Because this type of TTI does not require activation, it must be shipped from the manufacturer on dry ice or under frozen conditions and stored at temperatures according to the manufacturer's instructions, normally below –24° before use. Chemical polymerization-based TTIs can be designed to reach the end point as quickly as weeks at refrigerated temperature or as long as years at controlled room temperature.

Chemical Enzyme–Based Time–Temperature Indicators

This type of TTI uses an enzyme-catalyzed color-generating reaction that occurs as a function of time and temperature. The color change is caused by an enzyme reacting with a substrate, accompanied by a change in pH. The enzyme and substrate are in separate solutions in adjacent compartments. Breaking the barrier between the two compartments and mixing the two solutions activates the TTI.

¹¹ PDA Technical Report 53 (TR 53) Guidance for Industry: Stability Testing to Support Distribution of New Drug Products, <https://store.pda.org>.

¹² ASTM F1416–96 (2008) Standard Guide for Selection of Time Temperature Indicators.

Chemical–Organic Pigment–Based Time–Temperature Indicators

This type of TTI uses an organic pigment that is activated by exposure to ultraviolet light to develop a dark blue starting color. A filter is then placed over the label to protect it from deliberate or accidental reactivation. The colored pigment fades over time as a function of temperature.

RELATIVE HUMIDITY MEASUREMENT TECHNOLOGIES

Relative humidity is the ratio of the partial pressure of water vapor in air to the vapor pressure of saturated air at a given temperature. In other words, the relative humidity is the amount of water vapor present, divided by the theoretical amount of moisture that could be held by that volume of air at a given temperature. Extensive tables of relative humidity data are available. Devices for measuring relative humidity are called hygrometers. Several different technologies exist for measuring relative humidity.

Sling Psychrometer

The simplest type of hygrometer is based on the temperature difference observed between two identical thermometers, one ordinary and one with a wet cloth wick over its bulb. The two thermometers are whirled at the end of a chain, and the evaporation of water from the wick cools (based on evaporative cooling) the wet-bulb thermometer. The temperature difference between the wet and dry thermometers then is compared to a table specific to that psychrometer based on dry-bulb temperature, and the relative humidity is determined.

Hair Hygrometer

This type of device is based on the fact that the length of a synthetic or human hair increases as a function of the relative humidity. This change is used to move an indicator or affect a strain gauge. A hair hygrometer can be accurate to $\pm 3\%$, but it is unable to respond to rapid changes in humidity and loses accuracy at very high or very low levels of relative humidity.

Infrared Hygrometer

This type of hygrometer determines relative humidity by comparing the absorption of two different wavelengths of IR radiation through air. One wavelength is absorbed by water vapor and the other is not. This type of hygrometer can accurately measure relative humidity in large or small volumes of air. It is sensitive to rapid changes of humidity and can be integrated with an electronic data-handling system.

Dew Point Hygrometer

This type of device uses a chilled mirror to determine the dew point of an air sample. The dew point is the temperature at which water vapor in the air begins to condense; that is, the temperature at which the relative humidity is 100%. The relative humidity can be calculated from this measurement and an accurate measurement of the ambient temperature. The dew point hygrometer is the standard against which most commercially available instruments are calibrated.

Capacitive Thin-Film Hygrometer

The principle of this type of hygrometer is that the dielectric of a nonconductive polymer changes in direct proportion to the relative humidity. This change is measured as a change in capacitance. This type of hygrometer is accurate to $\pm 3\%$.

Resistive Thin-Film Hygrometer

This type of hygrometer is similar to the capacitive thin-film type because it uses the effect of changing relative humidity on an electric circuit. In the resistive thin-film hygrometer the sensor is an organic polymer whose electrical resistance changes in logarithmic proportion to the relative humidity. This type of hygrometer is accurate to $\pm 5\%$.

CALIBRATION OF TEMPERATURE- AND HUMIDITY-MONITORING DEVICES

Thermometers and hygrometers that are used to provide data about the temperature and humidity exposure of a product must be suitable for their intended use. Specifically, they must be appropriately calibrated. A calibration program assures the user of the monitoring device that the device has been tested before use either by the manufacturer or the user to assess the suitability for its intended use. Calibrations should be performed with appropriate frequencies to support ongoing use. Monitors used in manufacturing, storage, and transport of drug products should be properly qualified by their users to ensure that the monitors have been received and maintained in proper working order. It is acceptable to use the calibration performed by the device's manufacturer based on the certificate of calibration and expiration date.

For temperature- and humidity-monitoring devices, measurement accuracy refers to the closeness of the value obtained with a particular device and the true value of the object or environment under measurement. In practice, this is determined by comparison with a device that has been calibrated against a standard that is obtained from or is traceable to the National Institute of Standards and Technology or a comparable national metrology organization.

Any monitor takes time to respond to a change in the temperature or humidity. Measurement responsiveness typically is defined in a device's specifications for its operating range. Different data recording intervals are appropriate for different monitoring applications and should be based on supply chain length (for example, transportation via ocean may require 30-min intervals, but 15-min intervals may be suitable for air transport). Most commonly, time accuracy is expressed as a \pm percentage of total duration of the recording period. For pharmaceutical applications, a $\pm 0.5\%$ time accuracy is adequate.

Single-use electronic and chemical indicators should follow Good Manufacturing Practices with appropriate testing controls. Electronic indicators require proper calibration. Single-use indicator performance can be qualified by the supply chain user by sampling and testing of multiple production lots. For TTIs that calculate MKT, the performance of a batch can be assessed statistically by subjecting an appropriately sized sample to elevated temperature conditions for a set period of time and observing the results. Manufacturers should adopt appropriate acceptance criteria. It is acceptable to use the release test performed by the manufacturer of the indicator (based on the certificate of calibration or the certificate of analysis and the expiration date) in lieu of calibration or qualification.

THE USE OF HISTORICAL TEMPERATURE DATA

Although historical geographic and seasonal trends may be used as a planning tool in selecting among the types of temperature- and humidity-monitoring devices, outside ambient temperatures are not necessarily reliable indicators of the temperatures experienced by different items in the distribution chain. For example, studies have reported important departures from ambient temperatures on summer days for mailboxes, trucks, and warehouses.¹³ Therefore, using lane-specific temperature monitoring is beneficial when manufacturers and shippers develop an ambient profile and can be a valuable consideration for a risk-based approach to maintain product quality.¹⁴

A drug product's quality (identity, strength, and purity) may be notably influenced by variations in temperature and humidity over the course of its shelf life, so manufacturers should appropriately monitor those environmental conditions. Pharmaceutical manufacturers perform stability testing to carefully evaluate the effects of temperature and humidity on their products. The packaging, shelf life, and storage and transportation conditions recommended for a product are chosen based on the results of these stability studies. Temperature effects can happen rapidly; therefore, temperature monitoring should be implemented on a risk-based approach taking the product stability, distribution route, mode of transportation and potential risks that may compromise the quality of the product into account. Relative humidity effects occur over a much longer time frame; humidity monitoring can be omitted when the drug product is sufficiently protected by the primary container proven by sound stability studies. Humidity monitoring is recommended when special environmental restrictions concerning the humidity are defined for the drug product. ■¹⁵ (USP36)

- *Gaseous Sterilization* <1229.7>
- *Dry Heat Sterilization* <1229.8>
- *Physicochemical Integrators and Indicators for Sterilization* <1229.9>
- *Radiation Sterilization* <1229.10>
- *Vapor Phase Sterilization* <1229.11>

In the strictest definition of sterility, a specimen is deemed sterile only when there is a complete absence of viable microorganisms (bacteria, yeasts, and molds), but sterility cannot be demonstrated with respect to compendial articles and other items because of the inherent limitations of the current test (see *Sterility Tests* <71>). Sterility, therefore, is defined in probabilistic terms that establish an acceptable level of risk. Sterility can be accomplished only by the use of a validated sterilization process under appropriate current good manufacturing practices and cannot be demonstrated by reliance on sterility testing alone. The basic principles for control of sterilization processes, including method development, validation, and ongoing assurance, are as follows:

1. Sterilization process development that includes evaluation of the stability and compatibility of materials, container integrity, expected presterilization bioburden, equipment method control parameters, etc.
2. Identification of sterilization process parameters that preserve the inherent properties of the materials yet inactivate or remove microorganisms.
3. Demonstration that the sterilization process and equipment are capable of operating within the prescribed parameters and corresponding to independent measurements of the critical parameters.
4. Performance of replicate studies that represent the operational range of the equipment and employ actual or simulated product. The use of biological indicators for correlation between the measured physical parameters and the expected lethality is recommended wherever possible.
5. Maintenance and monitoring of the validated process during routine operation.
6. Assurance that the bioburden (number and type) of the materials is acceptable and is maintained within predetermined limits during routine operation.

Add the following:

■<1229> STERILIZATION OF COMPENDIAL ARTICLES

BACKGROUND AND SCOPE

This general information chapter provides an overview of the concepts and principles involved in sterilization (by various modes) of compendial articles that must be sterile. It includes information about supportive sterilization processes utilized in their preparation.¹ More detailed recommendations are presented in specific information chapters for each sterilization mode:

- *Steam Sterilization by Direct Contact* <1229.1>
- *Moist Heat Sterilization of Aqueous Liquids* <1229.2>
- *Monitoring of Bioburden* <1229.3>
- *Sterilizing Filtration of Liquids* <1229.4>
- *Biological Indicators for Sterilization* <1229.5>
- *Liquid Phase Sterilization* <1229.6>

¹³ Okeke, C.C. Medwick, T., Bailey, L.C., and Grady L.T. Temperature and Humidity Conditions During Shipment in International Commerce, *PF* 25(2) Mar.–Apr. 1999.

¹⁴ ISTA 7E Standard, <http://www.ista.org>.

¹⁵ These processes may also provide depyrogenation, the extent of which depends on the actual sterilization conditions. (Depyrogenation by various means will be addressed in a chapter under development.)

VALIDATION OF STERILIZATION PROCESSES

Validation of sterilization processes requires knowledge of sterilization technology and use of the appropriate instrumentation and equipment to control and verify critical sterilization process parameters. An important aspect of the sterilization validation program involves the use of biological indicators when appropriate. All sterilization processes should be maintained in a state of validation that includes periodic requalification. The validation program for each type of sterilization comprises several formally documented stages.

The general principles of validation programs are applicable to all sterilization procedures. Individual details are presented in the specific *USP* informational chapters for each sterilization mode.

The *process development* stage investigates and establishes the operating parameters that define the controls that will be used for the sterilization process. Portions of the cycle development can be performed in a laboratory setting. The *installation qualification* stage establishes that equipment controls and other instrumentation are installed as specified and calibrated. Documentation should demonstrate the acceptability of the required utilities such as steam, water, and air. The *operational qualification* stage confirms that the equipment functions within the defined sterilization parameters. The *performance qualification* stage of the validation program directly evaluates the sterilization of materials or articles. This determination requires independent parameter measurement during the sterilization process, as well as biological challenges in operational configurations. Correlation between the physical measurements and the demonstrated

microbiological lethality or removal capability for sterilizing filtration methods supports the effectiveness of the sterilization process. The *routine process control* stage of the sterilization process requires a number of supportive practices and is outlined in detail below.

ESTABLISHING AND JUSTIFYING STERILIZATION PROCESSES THAT RELY ON MICROBIAL INACTIVATION

Articles intended to be sterile must attain a $\leq 10^{-6}$ probability of a nonsterile unit, i.e., less than or equal to one chance in one million that viable *bioburden* microorganisms are present. [NOTE—This is also called the Sterility Assurance Level. The term *Probability of a Nonsterile Unit* (PNSU) is used throughout this chapter because it is descriptive and substantially easier to understand.] This PNSU can be accomplished by balancing the method effect on the materials and the destruction of the bioburden (see *Figure 1*). Three methods are currently in use: overkill, bioburden/biological indicator, and bioburden-based methods. These methods are described in greater detail below. Regardless of the method chosen, the objective is a maximum PNSU of $\leq 10^{-6}$ for the bioburden. An overkill method is the simplest method to establish but has the greatest impact on materials. The bioburden-based method requires the most method control but subjects the materials to the least stressful conditions. Confidence in the process's lethality is the same, regardless of the method utilized.

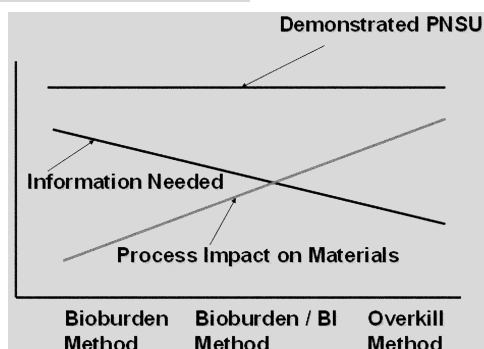


Figure 1. A basic comparison of various validation methods.

For items that are essentially unaffected by the sterilization process, the overkill method is preferred because of its simplicity. Overkill sterilization can be defined as a method in which the destruction of a high concentration of a resistant microorganism supports the destruction of reasonably anticipated bioburden present in routine processing. That objective can be demonstrated by attaining any of the following: a defined minimum lethality; a defined set of method conditions; or confirmation of minimum log reduction of a resistant biological indicator.

If articles could be damaged by extended exposure to the sterilization process, it may not be feasible to employ an overkill method. In these instances, demonstrating the effectiveness of the sterilization cycle requires not only information about the delivered method conditions but also knowledge about resistance and control of the population of the materials' bioburden. This method is widely used for the terminal sterilization of heat-labile solutions and laboratory media. This sterilization strategy is variously called the bioburden/biological indicator or combination based method and is defined thus:

Bioburden/biological indicator based sterilization is an approach in which the incomplete destruction (or destruction of a modest population) of a resistant biological indicator can be used to demonstrate the capability of the method to reliably destroy the bioburden present. This is accomplished using detailed knowledge of the bi-

oburden and biological indicator populations and their relative resistance.

The bioburden-based method is used when material stability is limited or when there are no suitable biological indicator microorganisms available to use with the sterilizing process. Customarily, radiation sterilization is validated using the bioburden based method. The bioburden-based method can be defined as:

A method in which bioburden samples from the material are routinely evaluated for resistance to the sterilization process and may be utilized to demonstrate the effectiveness of the process. Routine monitoring of the bioburden population and its resistance to the sterilization process is mandatory.

Filter sterilization of liquids and gases differs from other sterilization modes because filtration relies on removal of microorganisms from the fluid rather than inactivation by chemical or physical means.

D-Value and Microbial Resistance

The D-value is the time (customarily in minutes) or radiation dose (customarily in kGy) required to reduce the microbial population by 90% or 1 log₁₀ cycle (i.e., to a surviving fraction of 1/10) and must be associated with the specific lethal conditions at which it was determined (see *Figure 2*). For steam and dry heat, the D-value is a function of temperature. In gas sterilization (ethylene oxide, ClO₂, or O₃), D-values are a function of the chemical concentration, relative humidity, and temperature. Similarly, for liquid chemical sterilization the D-value is a function of the temperature and sterilant concentration. [NOTE—Determining the D-value for vapor (condensing) systems such as H₂O₂, H₂O₂ plasma, and peracetic acid is complex because of the biphasic nature of the materials. Radiation and filtration sterilization are validated using unique methods. These processes are validated by methods that differ from those in this introductory chapter.]

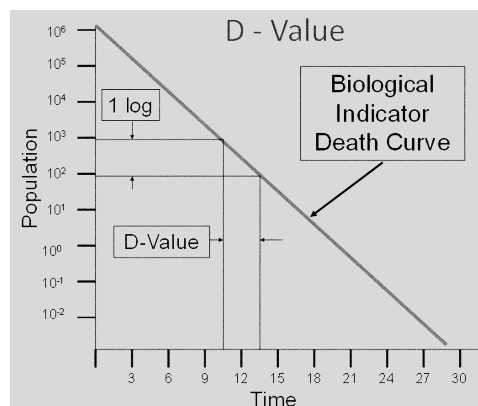


Figure 2. Graphical representation of D-value.

The D-value is not an inherent attribute of the microbe only, so the influence of other factors such as substrate, matrix, recovery media, and test methodology must be considered in D-value determination. The resistance of a biological indicator is defined for the indicator as a system. Accurate assessment and comparison between D-values requires standardization of test methods. To properly evaluate the effectiveness of a sterilization process, analysts must evaluate the resistance of the bioburden experimentally or via a literature search.

The death curve for microorganisms subjected to a sterilization process is comprised of three distinct regions (see *Figure 3*):

1. *Survivor curve region*—Where viable microorganisms can be recovered and counted to determine the slope of the death curve. Using survivor counts in short ex-

posure periods, the first section of the death curve can be drawn to where the population is approximately 10^3 CFU.

2. *Fraction negative region*—Where replicate studies with multiple biological indicators are used to estimate the slope. This can extend the demonstrable portion of the death curve to approximately 10^{-2} to 10^{-3} .
3. *Estimated region*—Where the death rate curve established by either the survivor curve method or fraction negative method is extrapolated to the desired PNSU. Below 10^{-3} the death curve is assumed to be linear and is depicted in Figure 3 by the dashed line beyond the point assuming that the death of microorganisms continues at the same rate.

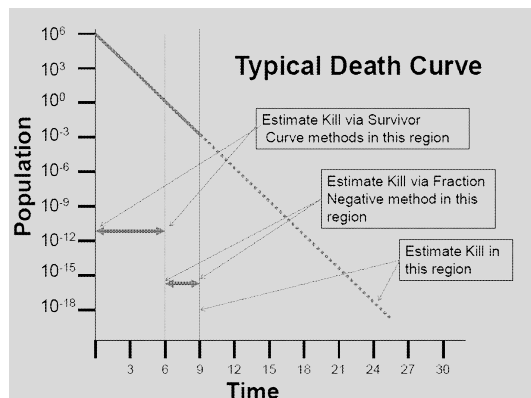


Figure 3. Death curve showing the various regions.

As stated earlier, the goal of the sterilization process is inactivation of the bioburden without adversely affecting product quality attributes. Demonstration of the lethality of a sterilization process under routine operation relies on differences in the relative resistance and population of the bioburden relative to the biological indicator (see Figure 4). Where the overkill method is used, bioburden controls can be less rigorous.

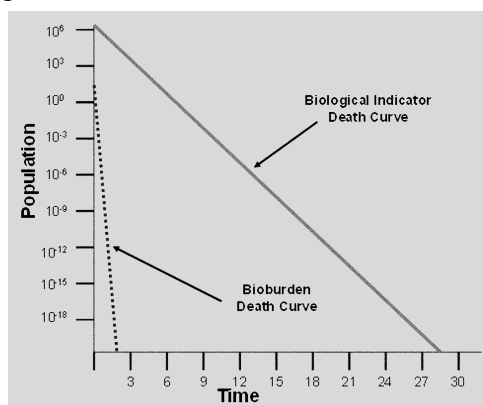


Figure 4. Relative resistance and population of typical biological indicator and bioburden microorganisms.

Validation of sterilization processes links physical measurements with biological indicator performance to establish method lethality. [NOTE—In radiation sterilization bioburden response is linked to physical irradiation dosage measurements.] Knowledge of the method's effectiveness coupled with bioburden controls on the materials under processing and information on bioburden resistance allow determination of the probability of a nonsterile unit.

Analysts must know the resistance of the biological indicator to the process in order to ensure that the organism's response to the process is properly understood. Equally important is an understanding of the bioburden present dur-

ing routine use of the sterilization process and its possible resistance to the chosen process.

Biological and Physical Data

The biological indicator, when used, is a convenient means to simplify the sterilization validation effort. Biological indicators customarily are bacterial spores that have established resistance to the sterilization process under evaluation. When supplied as spores (on a substrate or as a suspension) with known initial population and resistance, their response to the method can be correlated to the measured physical conditions. Spores are preferable as biological indicators because their resistance and population are predictable and stable when they are handled, stored, and used as recommended.

The spores can be placed in the sterilization load in locations where physical parameter measurements such as temperature or gas concentration cannot be easily obtained (e.g., within needle lumens, syringes, and ampuls) or where measurement may alter the delivered conditions (e.g., sampling of the lethal gas). The biological indicator provides a means to directly assess the sterilizing effect of the method in a manner not possible by physical measurements. The lethality-based physical measurement and biological inactivation data from a sterilization process should be in reasonable agreement. When this is not the case, an investigation should be considered.

STERILIZATION INDICATORS AND INTEGRATORS

The execution of sterilization processes can be supported by physical and chemical indicators and integrators that provide an indication that processing is completed. These are available in many different forms for use in conjunction with many common sterilization processes.

Sterilization indicators respond to sterilization process parameters in a nonquantitative fashion; i.e., they show passing or failing results. They are useful in an operating environment as a means to identify whether an item has been exposed to a sterilization process. They are of minimal use in directly establishing process efficacy. Sterilization integrators are more sophisticated devices that react quantitatively in response to one or more of the critical sterilization parameters and yield a result that can be correlated to lethality. The most sophisticated integrators are radiation dosimeters that are so accurate and robust that their use has displaced the use of biological indicators for the validation of radiation sterilization. Additional detail about integrators and indicators can be found in *Sterilization—Chemical and Physicochemical Indicators and Integrators* (1209).

STERILIZATION PROCESS DEVELOPMENT

An important consideration in any sterilization activity is the selection of an appropriate process from the many possible alternatives: steam, dry heat, gas, radiation, vapor, chemical, or filtration. The choice of the appropriate method for a given item requires knowledge of the sterilization process and information concerning effects of the process on the material being sterilized. The selection of a particular sterilizing treatment and the details of its execution often represent a compromise between the conditions required to destroy or remove the bioburden to the desired level and the impact of the sterilization process on the materials being processed. Sterilization processes should be sufficiently robust for certainty of microbial inactivation while avoiding adverse consequences to material quality attributes.

The overkill method employs conditions that are capable of destroying a high concentration of a resistant biological

indicator and thus are a greater challenge to material integrity and stability. Overkill is employed only where the items being sterilized can withstand extended exposure to the sterilizing process and is used most commonly for metal, glass, and other items that are unaffected by process exposure. Its use is always preferable where materials can tolerate the more aggressive conditions utilized.

The half-cycle validation method is a special case of the overkill method in which a lethal cycle to the biological indicator is arbitrarily doubled. Its use unnecessarily exposes materials to harsh conditions, and it should be avoided.

Bioburden/biological indicator (or combination) methods are appropriate when the product has some sensitivity to the sterilizing conditions. Analysts commonly use it for large- and small-volume parenterals, in-process solutions, and laboratory media for which the material properties would be impaired by a lengthy exposure to the sterilizing conditions. The proper use of the method requires control over the presterilization bioburden levels and confidence that the bioburden's resistance is such that it will be destroyed during processing. The complete destruction of or the use of a high population of the bioburden/biological indicator is not necessary for use of this method because it relies on differences in the relative resistance and population of the biological indicator and bioburden microorganisms.

The bioburden method bases the sterilization duration solely on the expected population and resistance of the bioburden on the materials. This is the method of choice for all radiation sterilization. It relies on periodic bioburden monitoring and resistance screening to establish confidence in the method. The bioburden method does not require use of a biological indicator.

Filtration is used for liquids and gases that either will not withstand heat, radiation, or chemical sterilization processes or are more conveniently sterilized in-line.

ROUTINE PROCESS CONTROL

After a sterilization process has been initially validated, it must be maintained in that state to ensure continued acceptable operation. This is accomplished by a number of related activities that are essential for continued use of the method.

Calibration—Equipment instrumentation must be periodically calibrated against a traceable standard. This includes recording as well as controlling instruments that regulate the operation of the equipment.

Physical Measurements—Data reported by the equipment sensors and recorders must be verified after the completion of each sterilization cycle. The records from the sterilization equipment are an essential part of the documentation.

Physical Integrators/Indicators—When they are used, integrators, and to a lesser extent indicators, provide an immediate indication of method execution and differentiate between processed and unprocessed materials. When these integrators provide a direct indication of method lethality (e.g., radiation dosimeters), they can be used for material release.

Parametric Release—The release of finished products without sterility testing is addressed in *Terminally Sterilized Pharmaceutical Products—Parametric Release* <1222>. **Additional Considerations**—Depending on the specifics of the particular sterilization process, there may be additional requirements for confirming method efficacy. These can include bioburden sampling, bioburden resistance determination, biological indicator resistance determination, and supplier audits. As applicable, these activities should be carried out to maintain the sterilization process in a validated state.

Change Control—To maintain a validated state, materials, procedures, and equipment that influence the sterilization process should be monitored to ensure that all changes are recorded and evaluated in terms of their potential impact. To accomplish this, analysts must establish a formalized system for change control.

Preventive Maintenance—The user should establish a defined preventive maintenance program for each piece of sterilizing equipment in accordance with the equipment manufacturer's written recommendation. Preventive maintenance represents a special class of predefined changes that have no adverse effects on the operation of the system and thus do not require evaluation under change control.

Periodic Reassessment—In the absence of change to the materials, method, or equipment, the effectiveness of sterilization processes should be reconfirmed on a periodic basis. This system should be formalized and should address the potential impact of a number of de minimus changes or undetected changes to the validated system. In the absence of change, the amount of information required to support a sterilization process is less than that required for initial acceptance of the sterilization process.

Training—Sterilization processes rely heavily on scientific principles for the effective destruction of microorganisms. Scientists and engineers well-grounded in the principles of microbial death and removal develop processes to ensure effective sterilization. Individuals involved in the development of sterilization processes require a background in microbiology, physics, chemistry, and engineering, and they must be familiar with good manufacturing principles and regulations. Sterilization is an interdisciplinary activity where the combined knowledge of a group of individuals is generally required for the establishment of a reliable process. In addition to the sterilization process development team, individuals responsible for maintenance and operation of sterilization processes must also be trained appropriately to ensure that their actions contribute to success. These individuals are often the first to identify upsets and shifts in process performance because of their intimate involvement with it. Effective training programs should be established and documented. Training programs should emphasize sterilization principles, adherence to established processes and procedures, and the importance of documenting deviations from normal operations.

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Add the following:

■(1229.1) STEAM STERILIZATION BY DIRECT CONTACT

SCOPE AND BACKGROUND

Steam sterilization is perhaps the most common of all sterilization processes. It is used in settings ranging from practitioner offices to large-scale manufacturing facilities. The diversity of practices that use steam sterilization is reflected in the range and sophistication of the equipment used. This general information chapter addresses sterilization in which saturated steam comes into direct contact with the load items (whether wrapped or unwrapped) and provides an overview of the basic concepts of this mode of sterilization, including its validation. The load items in this sterilization process are variously termed parts, components, hard goods, wrapped goods, or porous goods. These items may be metallic, glass, ceramic, elastomeric, or polymeric materials that have little or no sensitivity to thermal degradation at the sterilizing temperatures. For steam sterilization by direct contact, it is customary to sterilize items using an overkill method.

Sterilization of liquid-filled containers may be substantially different. *Moist Heat Sterilization of Aqueous Liquids* (1229.2) provides information about applications in which steam is a heating medium but is not in contact with the sterilization target, the liquid in the container.

SATURATED STEAM

Saturated steam is a biphasic mixture of H_2O in gas and liquid phases in thermal equilibrium. Saturated steam has a singular temperature–pressure relationship in which both phases are present, and at a given temperature only one pressure is possible for saturation. The importance of using saturated steam for sterilization arises primarily from two attributes. First, saturated steam rapidly kills microorganisms because of the presence of liquid water. Steam heated above saturation, also termed superheated steam, lacks liquid water, and although it is higher in temperature than saturated steam it is substantially less lethal to microbes. Second, when steam changes phase from gas to liquid, it releases thermal energy (2202 kJ/kg at 121°) that is transferred to the load items, facilitating sterilization of their exposed surfaces.

The initial objective for saturated steam sterilization is that the air in the sterilizing chamber must be replaced by saturated steam. Residual air within the sterilizer chamber and load items acts as both an insulator and an obstacle to steam penetration to all surfaces of the load items, and its removal is essential for effective sterilization. The presence of residual air in the chamber negates the singular temperature–pressure relationship of saturated steam. In the absence of saturation, physical measurements may not provide assurance of lethality.

GRAVITY DISPLACEMENT CYCLES

In the simplest autoclave cycles, air removal is accomplished by gravity displacement. Because steam is hotter and less dense than air, it rises to the top of the autoclave, and the colder air exits at the bottom of the chamber. Saturated steam entering the chamber changes into liquid con-

densate as it contacts the colder surfaces of the autoclave chamber and load items. Retention of condensate within the load reduces cycle effectiveness because it is a barrier to steam contact, and additional steam is needed to maintain the saturated steam at the sterilizing temperature. The load items, wrapping materials, and load arrangement should be designed to facilitate air removal and condensate drainage. In gravity displacement cycles, the load slowly reaches the desired sterilizing temperature because air removal is relatively slow compared to cycles in which its removal is mechanically assisted. During the exposure segment of the cycle, a thermostatic trap at the bottom of the chamber drain allows the removal of condensate (and any residual air) from the sterilizer while maintaining sterilizing conditions. At the conclusion of the dwell period, the chamber is returned to atmospheric pressure.

PREVACUUM CYCLES

To remove air more effectively from the chamber and the load items, sterilizers may employ multiple evacuation/pressure pulses in which air is replaced by steam. The number and depth of these pulses may vary. Because the alternating vacuum and pressure pulses may stress wrapping materials, the latter must be chosen carefully. The operation of the sterilizer during the exposure segment is similar to that of the gravity displacement cycle previously described. The vacuum system can be used at the end of the process to remove residual steam and condensate from the load items. The selection of a specific cycle and its associated sterilization parameters for a given item depends on a number of factors, including the heat lability of the material, heat penetration into the article, the item's mass, difficulties with air/condensate removal, and other factors described in the validation program (see below).

STERILIZATION CYCLE CONTROL

Sterilizers are controlled by computerized/automated systems that manage the overall process execution and data reporting. The systems for steam sterilization may be controlled by calibrated temperature and/or pressure sensors on the equipment. During the exposure portions of the cycle, a minimum dwell time at a predefined temperature is required to ensure the method lethality target (minimum time–temperature or F_0) is met. Cycle efficacy for steam sterilization often is measured using F_0 , which is defined as the equivalent exposure time at 121°. F_0 is a means for quantifying steam sterilization effectiveness by determining the equivalent sterilization time in minutes relative to a base temperature of 121° and a z-value of 10°; z-value is defined as the number of degrees of temperature change necessary to change the D-value by a factor of 10. The F_0 method is used to evaluate sterilization processes operated at varying temperature conditions to a single standard.

The process lethality at temperatures other than 121° can be calculated to determine lethality equivalent to that provided at 121°. Moist heat sterilization process efficacy is not intrinsically linked to a target temperature of 121°, which is simply the Celsius conversion of 250°F, and other temperatures can be used. Sterilizer control systems for direct sterilization typically provide a minimum time at a defined set point temperature after the initial air/condensate removal. Steam sterilizers are controlled using temperature sensors located in the drain line before the thermostatic trap, although other control schemes may be used. The temperature at this location typically is recorded for permanent documentation of sterilizing conditions. In sterilization by direct contact, exceeding the minimum time–temperature requirements or F_0 is acceptable because of minimal adverse consequences to the materials being sterilized.

Total lethality can be calculated over the course of the process. For the specific reference temperature of 121° and

a z-value of 10°, the total accumulated F_0 can be determined by the following equation:

$$F_0 = \int_{t_1}^{t_2} 10^{\left(\frac{T-121}{10}\right)} dt = \sum_{t_1}^{t_2} 10^{\left(\frac{T-121}{10}\right)} \Delta t$$

where

t_1 = start time

t_2 = end time

T = temperature

Summing the instantaneous lethality contributions over the entire sterilization process allows the calculation of the overall process lethality or F_0 delivered. The F_0 calculation should begin at 100° and should continue through the end of the dwell period provided that saturated steam conditions are maintained.

VALIDATION OF STERILIZATION BY DIRECT CONTACT

The predominant approach for steam sterilization by direct contact is the overkill method defined in *Sterilization of Compendial Articles* <1229>. Overkill sterilization is a method in which the destruction of a high concentration of a resistant microorganism is correlated with the destruction of reasonably anticipated bioburden present during routine processing. That objective can be demonstrated by attaining any of the following: a defined minimum lethality (F_0), a defined set of physical conditions, or confirmation of a minimum log reduction of a resistant biological indicator.

The validation requirements for the overkill method are less onerous than those for other methods such as those based on bioburden or bioburden/biological indicators. When the load items can withstand substantial heat without adverse consequence, overkill is the method of choice for steam sterilization because of its ease of execution, reduced considerations for bioburden control, and overall simplicity.

Equipment Qualification

Equipment qualification is a predefined program that examines the equipment to confirm that it has been properly installed and operates as intended before the sterilization process. Equipment qualification can be separated into installation qualification and operational qualification, or can be considered joint installation and operational qualification. The qualification effort provides a baseline for the sterilizer's preventive maintenance and change control.

Empty Chamber Temperature Distribution

A common procedure to evaluate steam sterilizer installation is the evaluation of the empty chamber's performance. Each air removal method used in the sterilizer is evaluated by temperature measurement near the corners of the sterilizer chamber, near the controlling probe, and other locations as appropriate. The distribution of temperatures in the empty chamber should be determined only by sensors located in the chamber, and the temperatures of the chamber drain or outside the chamber proper are not directly relevant in this validation activity. Differences in the cycle dwell period can be ignored because only the shortest dwell period for each air removal method must be evaluated. The acceptance criteria for this test vary with the sterilizer's capabilities and customary use. Biological indicators are not required in the evaluation of empty chamber temperature distribution.

Component Mapping

Items that are steam sterilized can be quite complex and may have interior void volumes, obscured surfaces, crevices, and difficult-to-reach product contact surfaces that must be sterilized. The ability of saturated steam to penetrate the wrapping materials or containers and to reach the surfaces should be established for each item. Although this is relatively easy for simple items such as spatulas, beakers, and other simple geometric shapes, it can be substantially more difficult for filling assemblies, filter housings, tubing, and hoses. Analysts should conduct studies to determine cold spots in items to ensure that heat penetration takes place throughout the load items using thermocouples in contact with the item's surface. These studies can be performed in a laboratory setting and need not be repeated when the same item is sterilized in multiple autoclaves. During this evaluation, all load items should be wrapped and oriented in a manner that facilitates steam ingress and air and condensate removal. Items must be wrapped and oriented in an essentially identical manner for reproducible sterilization.

Load Mapping

The determination of loading patterns is an essential practice for terminal sterilization of aqueous liquids by moist heat (see *Moist Heat Sterilization of Aqueous Liquids* <1229.2>), but this practice is not a critical concern regarding direct sterilization of items because differences between components play a greater role than location within the load.¹ Loads for direct steam sterilization can be validated using a maximum and minimum load as determined by either the number of each item or their mass. Best practices include placing larger items on the lower shelves, allowing condensate from these items to exit the sterilizer with minimal contact with other load items.

Biological Indicators

The commonly used biological indicator for steam sterilization by direct contact contains spores of *Geobacillus stearothermophilus* (ATCC 12980 or ATCC 7953), a thermophilic microorganism with a moist heat resistance substantially greater than that of most vegetative microorganisms. The spore challenge can be placed on a substrate within or on a load item, or the challenge can be a load item that is inoculated with a spore suspension. When biological indicators are used according to the manufacturer's directions, the resistance information provided by the vendor can be used. End users must determine the population and resistance of inoculated items they prepare.

Heat Penetration and Microbiological Challenge

The goal of the validation activity is the confirmation of acceptable heat penetration using temperature measurements and biological indicator challenges. Customarily this study is performed under conditions where the exposure time and/or temperature are reduced slightly from the routine set points. Thermocouples and biological indicators should be placed with load items at the locations determined to be most difficult to heat during component mapping. Thermocouples should be in contact with the item's surface. Analysts must take care in the insertion of thermocouples and biological indicators so they do not alter the ability of the steam to enter the objects being challenged. This difficulty can be overcome with special fittings for ther-

¹ A Risk-Based Approach to Variable Load Configuration Validation in Steam Sterilization: Application of PDA Technical Report 1 Load Equivalence Topic. A. Pavell and K.A. Hughes. PDA J Pharm Sci and Tech 2010, 2010 Mar-Apr;64(2):124-136.

mocouple entry or by placement of temperature probes in units placed near the units that contain biological indicators. In the latter case, replicate studies provide proof of cycle efficacy when both the biological indicators are killed and the physical measurements correspond to the expected time–temperature values or F_0 . If the microbial and physical measurements do not meet predefined acceptance criteria, an investigation is required and corrective action is necessary to rectify the discrepancy.

Routine Process Control

As with all sterilization processes, after validation, steam sterilization must be subject to formal controls that maintain it in a validated state over time. *Sterilization of Compendial Articles* <1229> outlines the general requirements for all sterilization processes including training, calibration, physical measurements, physical integrators or indicators, ongoing method control, change control, preventive maintenance, and periodic reassessment.

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■1S (USP36)

Add the following:

■<1229.2> MOIST HEAT STERILIZATION OF AQUEOUS LIQUIDS

INTRODUCTION

Steam sterilization of aqueous liquids (including both suspensions and emulsions with mixing), also known as sterilization of nonporous loads, is the method of choice for aqueous parenteral products, in-process aqueous liquids, laboratory media, and biological waste materials. This type of sterilization is accomplished primarily in closed containers. During steam sterilization by direct contact (also called steam sterilization of parts, hard goods, or porous items) the steam in the chamber directly contacts the surface of load items to effect sterilization (see *Steam Sterilization by Direct Contact* <1229.1>). In contrast, sterilization of liquids in containers is accomplished by application of heat to the container, heating of the container wall, and ultimately heating of the internal liquid volume. This can be accomplished using steam, superheated water, and air in various combina-

tions. Some aqueous liquids are susceptible to over-processing that could render them unfit for their intended use. Manufacturers should consider the influence of these differences when they establish a suitable process.

During the sterilization of liquid-filled containers, differential pressures between the interior of the containers and the sterilization chamber may potentially impact container integrity. Air over-pressure is used to minimize the pressure differential between the container and the sterilizer to protect the integrity of the container, especially prefilled syringes and plastic containers. Before sterilization of product containers, manufacturers should consider the potential adverse consequences of excess heat on the materials. In order to ensure sterility as well as functionality, the process definition and validation method used must incorporate both lower and upper temperature and time limits on the process conditions.

When the overkill method can be used for sterilization of sealed liquid containers, it is the preferred method and is described in *Steam Sterilization by Direct Contact* <1229.1>. When product quality attributes can be impaired by excessive heat, the sterilization process should use less time or a lower temperature to minimize the adverse effect on the materials. Sterilization time–temperature or F_0 conditions (F_0 is defined as the equivalent sterilization time relative to a base temperature of 121°) include both lower (sterility-related) and upper (stability-related) limits.¹ Manufacturers commonly employ the bioburden/biological indicator (BB/BI) or bioburden methods when constraints on the material's ability to withstand the process require the use of less aggressive conditions. This approach requires appropriate controls on presterilization bioburden and/or product-related D-values in conjunction with bioindicators of lower spore count or resistance to ensure sterilization.

Terminal Sterilization of Products

The maintenance of product attributes may require the use of sterilizing conditions that are less aggressive and sterilization equipment, cycles, and validation methods adapted to these more restricted circumstances. The substantial variations in equipment designs and methods for terminal sterilization preclude a singular description of a typical cycle. All terminal sterilizers heat the load, but they accomplish this in varying ways: saturated steam; steam–air mixtures, steam–air–water mixtures, and superheated water. Air over-pressure for maintenance of container integrity and cooling containers and water for heating/cooling of the load may be present depending upon the autoclave size, throughput expectations, and container.

In-Process Fluids

In-process fluids are used for pH adjustment, dilution to a specified volume, lubrication, and other purposes. In many instances these liquids are sterilized in conjunction with items that must be sterilized by direct steam contact, and the sterilization process must ensure that all items are adequately sterilized.

Laboratory Media

Laboratory media often are sterilized in standard steam autoclaves with minor adaptations. Provision for slow exhaust (to reduce stress on container integrity and minimize boil over) and jacket cooling can help improve the basic steam sterilizer design and operation to better accommodate the materials. The sterilization process may be specific for media containers or a combination of both liquid-filled containers and hard goods. This process may resemble the methods used for terminally sterilized products (see above).

¹ Degradation kinetics may differ from those of microbial kill, and F_0 values may not be sufficient to fully evaluate “worst case” effects.

The sterilization of laboratory media may entail the processing of a number of different containers that contain different materials. Manufacturers should be aware of the potential for under- and over-processing across the load and must consider container size, container contents, and position. When liquid-filled containers are combined in the same load with hard goods, manufacturers must consider the unique concerns of each to ensure all items are properly sterilized. Because laboratory media are considered self-indicating with respect to sterility, the use of internal biological indicators during validation is not required.

Biowaste Sterilization

The sterilization of biowaste in sealed containers from laboratory or production use is similar to parts sterilization. The process is defined to ensure a minimum time–temperature exposure or attainment of a specified *F₀* value throughout all items of the load. Depending on the potential contaminants present, the autoclave design may incorporate condensate collection/sterilization or sterilizable exhaust filters to ensure that pathogens are adequately contained. Because the objective of biowaste sterilization is to render the materials safe for contact and disposal, the overkill method described in *Steam Sterilization by Direct Contact* (1229.1) is employed.

BIOBURDEN/BIOLOGICAL INDICATOR METHOD

Application of the BB/BI method requires a thorough understanding of the bioburden type, population, and resistance typically present in the presterilized product-filled container. The method relies on substantial differences between moist heat resistance and the population of the bioburden present and the biological indicator used during validation (Figure 1).

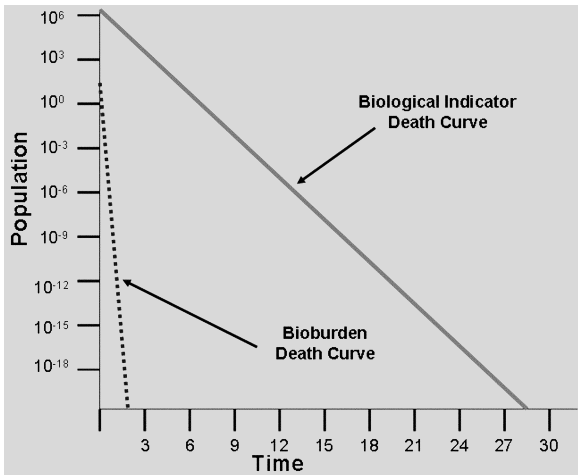


Figure 1. Relative resistance and population of typical bioburden and biological indicator microorganisms.

BB/BI is a method in which the incomplete destruction (or destruction of a modest population) of a resistant biological indicator can be used to demonstrate the capability of the process to reliably destroy any bioburden. This is accomplished using detailed knowledge of the BB and BI populations and their relative resistance.

Typical BB microorganisms have only minimal resistance in comparison to BIs, and this can be confirmed by heat screening of BB isolates. The BB population is controlled by filtration steps for the fluid, process time limits, environmental controls, gowning systems, and other means. The conventional BIs for terminal sterilization using the BB/BI method are *Clostridium sporogenes* ATCC 7955 and *Bacillus*

subtilis ATCC 5230, although other strains can be used. The use of *Geobacillus stearothermophilus* for terminal sterilization is uncommon with the BB/BI method because the organism’s strong resistance to moist heat makes it poorly suited for this application.

Confirmation of an acceptable probability of a nonsterile unit (PNSU) can be accomplished using physical measurements and BI response (which define the lethality of the process) in conjunction with processing limits for the BB population and resistance (which define the *N₀* and *D*-value). *D*-value is the time (customarily in minutes) required to reduce the microbial population by 90% or 1 log₁₀ cycle (i.e., to a surviving fraction of 1/10) and must be associated with the specific lethal conditions at which it was determined. For example, *D*₁₂₁ is the *D*-value at 121°. Articles intended to be sterile must attain a ≤10⁻⁶ PNSU, i.e., less than or equal to 1 chance in 1 million that viable bioburden microorganisms are present. The PNSU can be determined from Equation 1.

log *N_u* = −*F*/*D* + log *N₀* [1]

- N_u* = PNSU
- D* = *D*-value of the natural bioburden
- F₀* = *F₀*-value of the process (lethality)
- N₀* = bioburden population per container

The following example indicates the resulting PNSU under the defined conditions of validation and routine operation (Table 1).

Table 1. Examples of PNSU Calculation

Validation	Routine Usage
<i>F₀</i> = 8.0 min	<i>F₀</i> = 8.0 min
<i>D</i> ₁₂₁ of BI = 0.5 min	<i>D</i> ₁₂₁ of bioburden = 0.005 min
<i>N₀</i> of BI = 10 ⁶	<i>N₀</i> of bioburden = 100 (or 10 ²)
PNSU for BI = 10 ^{−10}	PNSU for BB = 10 ^{−1598}

Determining the resistance of the bioburden is accomplished using a heat-screening process during which a pure culture (a laboratory culture containing a single species of organism spores with minimal vegetative cells) is boiled at 100° for various periods. If the bioburden microorganism is viable after exposure, its resistance at 121° can be estimated for use in the PNSU calculation (Table 2).

Table 2. *D*₁₂₁ Estimation from Boil Test Results

Exposure Time	Approximate <i>D</i> ₁₂₁ -value
1 min	0.01 min
10 min	0.1 min
20 min	0.2 min
100 min	1.0 min

Bioburden Method

In most respects the BB method is similar to the BB/BI indicator method. The difference lies in the isolation and characterization of the most-resistant bioburden microorganism. The worst-case isolate is used as the biological indicator in the evaluation of the process. For use in this manner, it must be cultured to produce a suitable challenge population. When this method is used, the bioburden of each process cycle must be closely controlled with respect to population and must be monitored for resistance.

Sterilization Cycle Control

Process equipment for terminal sterilization typically is controlled by calibrated and pressure sensors in/on the chamber/equipment. During the exposure portions of the cycle, attainment of a minimum dwell time at a predefined

temperature is used to support process lethality. Cycle lethality for terminal sterilization customarily is measured using F_0 , which is defined as an actual exposure time at a variable process temperature that is equivalent to an exposure at 121° based on an ideal microorganism with a z-value of 10°. This can include lethality delivered during the heat-up and cooling phases of the sterilization process. A z-value is defined as the number of degrees of temperature change necessary to change the D-value by a factor of 10. The F_0 approach is used to evaluate to a single standard sterilization processes that are operated at varying temperature conditions. The process lethality at temperatures other than 121° can be calculated to determine lethality equivalent to that provided at 121°. Sterilizer control systems for terminal sterilization deliver conditions within a predefined time–temperature or F_0 range to avoid over-processing.

Simple mathematics can be used to calculate the total lethality over the course of the process. For the specific reference temperature of 121° and a z-value of 10.0°, the F_0 calculation can be determined by Equation 2:

$$F_0 = \int_{t_1}^{t_2} 10^{\left(\frac{T-121}{10}\right)} dt = \sum_{t_1}^{t_2} 10^{\left(\frac{T-121}{10}\right)} \Delta t \quad [2]$$

t = time

T = temperature

Summing the instantaneous lethality contributions over the entire sterilization process allows the calculation of the overall process lethality or F_0 delivered over the course of the entire process at varying conditions.

Validation of Liquid-Filled Container Sterilization

As previously noted, the preferred method for steam sterilization is the overkill method as defined in *Sterilization of Compendial Articles* (1229) and *Steam Sterilization by Direct Contact* (1229.1). However, when the processed materials are susceptible to damage by moist heat at the overkill conditions, the BB/BI method is better suited because it results in reduced heat input while affording the same degree of process efficacy but with different controls. As noted above, terminal sterilization processes require greater consideration of the effects of the treatment on material properties. This has implications for many of the elements of the qualification and validation exercises as indicated below. The validation requirements for the BB/BI and BB methods are more rigorous than those associated with the overkill method. Although the overkill method can be confidently used without detailed consideration of the presterilization bioburden, application of the BB/BI and BB methods require continued monitoring and control of the bioburden, specifically the population and resistance. This is accomplished by testing of filled containers just before sterilization and measuring the number of colony-forming units per container and confirming the absence of resistant BB isolates. When resistant isolates are found, their thermal resistance in the fluid should be determined.

Effect of the Sterilization Process—A preliminary determination of the liquid and the container–closure system's ability to withstand the expected sterilizing conditions should be made during product development. This can be accomplished by sterilization at conditions slightly in excess of the maximum expected and evaluating the effect on the material. The evaluation should encompass the essential quality attributes with attention focused on known and potential new impurities. Appearance and other physical properties also should be evaluated as a part of this effort.

Equipment Qualification—Equipment qualification is a predefined program that confirms the equipment has been properly installed and that it operates as intended. Qualification of the sterilizing equipment provides a baseline for preventive maintenance and change control for the sterilizer.

The sterilization equipment may require qualification of air, water, utility, and other systems that impact the sterilization equipment's performance.

Empty Chamber Temperature Distribution—The dual considerations of sterility and stability commonly associated with sterilization of liquids require that equal attention be paid to potential under- and over-processing of the load. For this reason the temperature gradient across the sterilizer may require substantially tighter control than that expected in sterilization by direct contact. The objective is to minimize the time–temperature or F_0 differences across the load throughout the process. Biological indicators are not required in the evaluation of empty chamber temperature distribution.

Biological Indicators—The selection of a BI must be considered carefully because of the balance that must be maintained between attaining sterilization and maintaining the sterilized material's essential quality attributes. The biological challenge is either directly inoculated into a liquid-filled container or is introduced via self-contained units provided there is adequate correlation between their resistance and the resistance that would occur in the process fluid. The liquid can be either the product or a surrogate fluid. The resistance of the indicator in the product (and surrogate fluid, where used) must be known. The surrogate's physical properties should approximate those of the product. If there are surfaces within the container that are not presterilized, biological challenge of those surfaces may be required.

Liquid D-Value Determination—Determination of the thermal resistance (D-value and z-value) for the biological indicator in the liquid is required. This must be performed in a Biological Indicator Evaluation Resistometer (BIER) in replicate. The thermal resistance of each BI lot in the liquid should be determined. When a surrogate liquid is used for convenience (e.g., a master solution approach) or because of microbial inhibition of the BI by the liquid, the thermal resistance in the surrogate must be determined.

Container Mapping—Liquid-fill containers with volumes greater than or equal to 100 mL should be mapped to determine internal cold spots. The mapping should be performed with product containers oriented as they would be within the load. The temperature probes should be introduced into the containers using methods that maintain container integrity. Internal supports (of minimally heat-conductive materials) may be required to ensure proper positioning of the probe within the container. After these locations are determined, they are used as either monitoring locations or are correlated to external conditions on the container during validation and routine processing. Smaller containers (less than 100 mL) have fewer discernable cold spots, the importance of which is reduced as container size decreases. Smaller containers (less than 100 mL) can be monitored with temperature probes secured to their exterior. The "cold spot" should be considered a "region" and not a single point in the container.

Load Positioning and Mapping—A fixed loading position within the sterilizer may be necessary for proper sterilization to ensure uniformity of heating and cooling in routine use. Once the load is positioned properly, its size can vary within a defined range. Load-mapping studies should be performed to determine the coldest and hottest locations within the load. These locations may not be specific individual containers but rather regions. This ensures that the containers are neither under- nor over-processed in routine operation of the sterilizer. Validation of variable-size load patterns is accomplished using a bracketing approach for which success with maximum and minimum loads (avoiding both under- and over-processing) establishes the acceptability of intermediate-size loads. However, evaluation of intermediate load sizes may be beneficial. In product sterilization, only a single-size container with a single product lot is processed concurrently.

Heat Penetration and Microbiological Challenge—The core of the validation activity is confirmation of acceptable heat penetration using temperature measurements and microbial challenge inactivation. Temperature probes and biological indicators are placed within the load at worst-case locations (e.g., the coldest portions of the loaded chamber). Introduction of the thermocouples must not alter the integrity of the container. Biological challenges are placed in containers adjacent to those that contain heat penetration probes (or the same unit with external temperature measurement).

Proof of cycle efficacy is provided by replicate studies in which the BIs perform as expected and the physical measurements correspond to the expected values of time and temperature or F_0 . If the microbial and physical measurements do not correlate, an investigation is in order, and corrective action must be taken to rectify the discrepancy. Samples from the hottest regions of the load are used for evaluation of material stability and quality.

Product Quality and Stability Evaluation—Manufacturers must conduct ongoing evaluation of the product's ability to withstand the routine sterilizing conditions. The evaluation should encompass the essential quality attributes with attention focused on known and potential new impurities and those materials that receive the most heat input. Manufacturers also should evaluate appearance, other physical properties, and container–closure integrity as a part of this effort. For microbiological media, the ability of the media to meet growth promotion and other requirements is required as indicated in the appropriate test chapter(s) (e.g., *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* <61>, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* <62>, and *Sterility Tests* <71>).

Routine Process Control

All sterilization processes should be subject to formalized practices that maintain them in a controlled state. The practices outlined in *Sterilization of Compendial Articles* <1229> include the general requirements appropriate for all sterilization systems. This is accomplished by a number of related practices that are essential for continued use of the process over an extended period of time. The practices include: calibration, physical measurements, physicochemical integrators, indicators for sterilization, monitoring of bioburden, ongoing process control, change control, preventive maintenance, periodic reassessment, and training.

The use of parametric release is common in the terminal sterilization of finished product containers. This subject is addressed in *Terminally Sterilized Pharmaceutical Products—Parametric Release* <1222>

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<1231> WATER FOR PHARMACEUTICAL PURPOSES

INTRODUCTION

Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical products, active pharmaceutical ingredients (APIs) and intermediates, compendial articles, and analytical reagents. This general information chapter provides additional information about water, its quality attributes that are not included within a water monograph, processing techniques that can be used to improve water quality, and a description of minimum water quality standards that should be considered when selecting a water source.

This information chapter is not intended to replace existing regulations or guides that already exist to cover USA and international (ICH or WHO) GMP issues, engineering guides, or other regulatory (FDA, EPA, or WHO) guidances for water. The contents will help users to better understand pharmaceutical water issues and some of the microbiological and chemical concerns unique to water. This chapter is not an all-inclusive writing on pharmaceutical waters. It contains points that are basic information to be considered, when appropriate, for the processing, holding, and use of water. It is the user's responsibility to assure that pharmaceutical water and its production meet applicable governmental regulations, guidances, and the compendial specifications for the types of water used in compendial articles.

Control of the chemical purity of these waters is important and is the main purpose of the monographs in this compendium. Unlike other official articles, the bulk water monographs (*Purified Water* and *Water for Injection*) also limit how the article can be produced because of the belief that the nature and robustness of the purification process is directly related to the resulting purity. The chemical attributes listed in these monographs should be considered as a set of minimum specifications. More stringent specifications may be needed for some applications to ensure suitability for particular uses. Basic guidance on the appropriate applications of these waters is found in the monographs and is further explained in this chapter.

Control of the microbiological quality of water is important for many of its uses. Most packaged forms of water that have monograph standards are required to be sterile because some of their intended uses require this attribute for health and safety reasons. USP has determined that a microbial specification for the bulk monographed waters is inappropriate, and it has not been included within the monographs for these waters. These waters can be used in a variety of applications, some requiring extreme microbiological control and others requiring none. The needed microbial specification for a given bulk water depends upon its use. A single specification for this difficult-to-control attribute would unnecessarily burden some water users with irrelevant specifications and testing. However, some applications may require even more careful microbial control to avoid the proliferation of microorganisms ubiquitous to water during the purification, storage, and distribution of this substance. A microbial specification would also be inappropriate when related to the "utility" or continuous supply nature of this raw material. Microbial specifications are typically assessed by test methods that take at least 48–72 h to generate results. Because pharmaceutical waters are generally produced by continuous processes and used in products and manufacturing processes soon after generation, the water is likely to have been used well before definitive test results are available. Failure to meet a compendial specifica-

tion would require investigating the impact and making a pass/fail decision on all product lots between the previous sampling's acceptable test result and a subsequent sampling's acceptable test result. The technical and logistical problems created by a delay in the result of such an analysis do not eliminate the user's need for microbial specifications. Therefore, such water systems need to be operated and maintained in a controlled manner that requires that the system be validated to provide assurance of operational stability and that its microbial attributes be quantitatively monitored against established alert and action levels that would provide an early indication of system control. The issues of water system validation and alert/action levels and specifications are included in this chapter.

SOURCE OR FEED WATER CONSIDERATIONS

To ensure adherence to certain minimal chemical and microbiological quality standards, water used in the production of drug substances or as source or feed water for the preparation of the various types of purified waters must meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the U.S. Environmental Protection Agency (EPA) or the drinking water regulations of the European Union or Japan, or the WHO drinking water guidelines. Limits on the types and quantities of certain organic and inorganic contaminants ensure that the water will contain only small, safe quantities of potentially objectionable chemical species. Therefore, water pretreatment systems will only be challenged to remove small quantities of these potentially difficult-to-remove chemicals. Also, control of objectionable chemical contaminants at the source-water stage eliminates the need to specifically test for some of them (e.g., trihalomethanes and heavy metals) after the water has been further purified.

Microbiological requirements of drinking water ensure the absence of coliforms, which, if determined to be of fecal origin, may indicate the potential presence of other potentially pathogenic microorganisms and viruses of fecal origin. Meeting these microbiological requirements does not rule out the presence of other microorganisms, which could be considered undesirable if found in a drug substance or formulated product.

To accomplish microbial control, municipal water authorities add disinfectants to drinking water. Chlorine-containing and other oxidizing substances have been used for many decades for this purpose and have generally been considered to be relatively innocuous to humans. However, these oxidants can interact with naturally occurring organic matter to produce disinfection by-products (DBPs), such as trihalomethanes (THMs, including chloroform, bromodichloromethane, and dibromochloromethane) and haloacetic acids (HAAs, including dichloroacetic acid and trichloroacetic acid). The levels of DBPs produced vary with the level and type of disinfectant used and the levels and types of organic materials found in the water, which can vary seasonally.

Because high levels of DBPs are considered a health hazard in drinking water, drinking water regulations mandate their control to generally accepted nonhazardous levels. However, depending on the unit operations used for further water purification, a small fraction of the DBPs in the starting water may carry over to the finished water. Therefore, the importance of having minimal levels of DBPs in the starting water, while achieving effective disinfection, is important.

DBP levels in drinking water can be minimized by using disinfectants such as ozone, chloramines, or chlorine dioxide. Like chlorine, their oxidative properties are sufficient to damage some pretreatment unit operations and must be removed early in the pretreatment process. The complete removal of some of these disinfectants can be problematic. For example, chloramines may degrade during the disinfection process or during pretreatment removal, thereby releas-

ing ammonia, which in turn can carry over to the finished water. Pretreatment unit operations must be designed and operated to adequately remove the disinfectant, drinking water DBPs, and objectionable disinfectant degradants. A serious problem can occur if unit operations designed to remove chlorine were, without warning, challenged with chloramine-containing drinking water from a municipality that had been mandated to cease use of chlorine disinfection to comply with ever-tightening EPA Drinking Water THM specifications. The dechlorination process might incompletely remove the chloramine, which could irreparably damage downstream unit operations, but also the release of ammonia during this process might carry through pretreatment and prevent the finished water from passing compendial conductivity specifications. The purification process must be reassessed if the drinking water disinfectant is changed, emphasizing the need for a good working relationship between the pharmaceutical water manufacturer and the drinking water provider.

Change to read:

TYPES OF WATER

There are many different grades of water used for pharmaceutical purposes. Several are described in *USP* monographs that specify uses, acceptable methods of preparation, and quality attributes. These waters can be divided into two general types: bulk waters, which are typically produced on site where they are used; and sterile waters, which are produced, packaged, and sterilized to preserve microbial quality throughout their packaged shelf life. There are several specialized types of sterile waters, differing in their designated applications, packaging limitations, and other quality attributes.

There are also other types of water for which there are no monographs. These are all bulk waters, with names given for descriptive purposes only. Many of these waters are used in specific analytical methods. The associated text may not specify or imply certain quality attributes or modes of preparation. These nonmonographed waters may not necessarily adhere strictly to the stated or implied modes of preparation or attributes. Waters produced by other means or controlled by other test attributes may equally satisfy the intended uses for these waters. It is the user's responsibility to ensure that such waters, even if produced and controlled exactly as stated, be suitable for their intended use. Wherever the term "water" is used within these compendia without other descriptive adjectives or clauses, the intent is that water of no less purity than *Purified Water* be used.

What follows is a brief description of the various types of pharmaceutical waters and their significant uses or attributes. *Figure 1* may also be helpful in understanding some of the various types of waters.

Bulk Monographed Waters and Steam

The following waters are typically produced in large volume by a multiple-unit operation water system and distributed by a piping system for use at the same site. These particular pharmaceutical waters must meet the quality attributes as specified in the related monographs.

Purified Water—*Purified Water* (see the *USP* monograph) is used as an excipient in the production of nonparenteral preparations and in other pharmaceutical applications, such as cleaning of certain equipment and nonparenteral product-contact components. Unless otherwise specified, *Purified Water* is also to be used for all tests and assays for which water is indicated (see *General Notices and Requirements*). *Purified Water* is also referenced throughout the *USP–NF*. Regardless of the font and letter case used in its spelling,

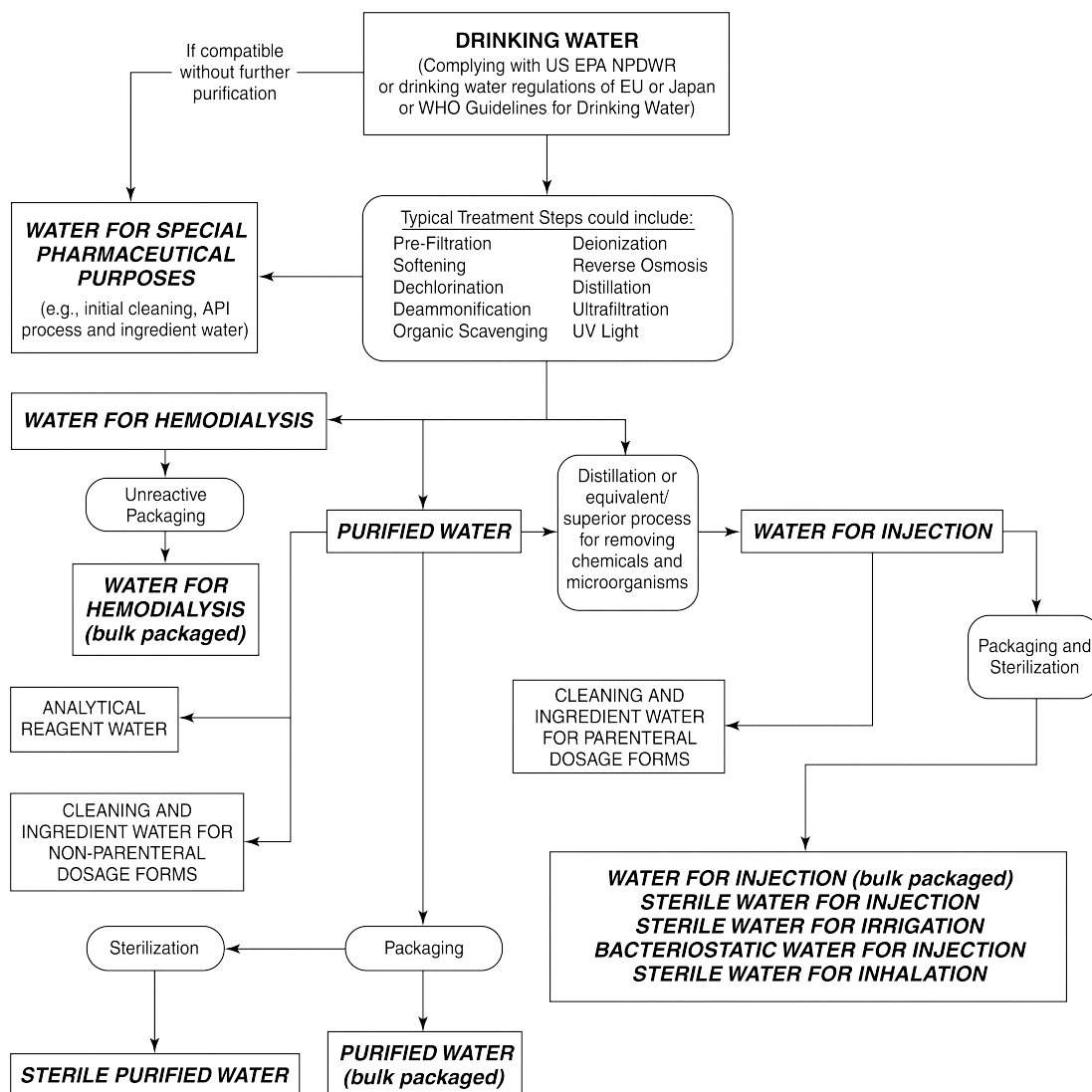


Figure 1. Water for pharmaceutical purposes.

water complying with the *Purified Water* monograph is intended. *Purified Water* must meet the requirements for ionic and organic chemical purity and must be protected from microbial contamination. The minimal quality of source or feed water for the production of *Purified Water* is *Drinking Water*. This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. Purified water systems must be validated to reliably and consistently produce and distribute water of acceptable chemical and microbiological quality. Purified water systems that function under ambient conditions are particularly susceptible to the establishment of tenacious biofilms of microorganisms, which can be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use.

The *Purified Water* monograph also allows bulk packaging for commercial use elsewhere. In contrast to *Sterile Purified Water*, bulk packaged *Purified Water* is not required to be sterile. Because there is potential for microbial contamination and other quality changes in this bulk packaged non-sterile water, this form of *Purified Water* should be prepared and stored in a fashion that limits microbial growth and/or is simply used in a timely fashion before microbial proliferation renders it unsuitable for its intended use. Also depending on the material used for packaging, there could be extractable compounds leaching into the water from the packaging. Although this article is required to meet the same chemical purity limits as the bulk water, packaging extractables will render the packaged water less pure than the bulk water. The nature of these impurities may even render the water an inappropriate choice for some applications. It is the user's responsibility to ensure fitness for use of this packaged article when used in manufacturing, clinical,

or analytical applications where the pure bulk form of the water is indicated.

Water for Injection—*Water for Injection* (see the *USP* monograph) is used as an excipient in the production of parenteral and other preparations where product endotoxin content must be controlled, and in other pharmaceutical applications, such as cleaning of certain equipment and parenteral product-contact components. The minimum quality of source or feed water for the generation of *Water for Injection* is *Drinking Water* as defined by the U.S. Environmental Protection Agency (EPA), EU, Japan, or WHO. This source water may be pretreated to render it suitable for subsequent distillation (or whatever other validated process is used according to the monograph). The finished water must meet all of the chemical requirements for *Purified Water* as well as an additional bacterial endotoxin specification. Because endotoxins are produced by the kinds of microorganisms that are prone to inhabit water, the equipment and procedures used by the system to purify, store, and distribute *Water for Injection* must be designed to minimize or prevent microbial contamination as well as remove incoming endotoxins from the starting water. *Water for Injection* systems must be validated to reliably and consistently produce and distribute this quality of water.

The *Water for Injection* monograph also allows bulk packaging for commercial use. In contrast to *Sterile Water for Injection*, bulk packaged *Water for Injection* is not required to be sterile. However, to preclude significant changes in its microbial and endotoxins content during storage, this form of *Water for Injection* should be prepared and stored in a fashion that limits microbial growth and/or is simply used in a timely fashion before microbial proliferation renders it unsuitable for its intended use. Also depending on the material used for packaging, there could be extractable compounds leaching into the water from the packaging. Although this article is required to meet the same chemical purity limits as the bulk water, packaging extractables will render the packaged water less pure than the bulk water. The nature of these impurities may even render the water an inappropriate choice for some applications. It is the user's responsibility to ensure fitness for use of this packaged article when used in manufacturing, clinical, or analytical applications where the purer bulk form of the water is indicated.

Water for Hemodialysis—*Water for Hemodialysis* (see the *USP* monograph) is used for hemodialysis applications, primarily the dilution of hemodialysis concentrate solutions. It is produced and used on site and is made from EPA Drinking Water that has been further purified to reduce chemical and microbiological components. It may be packaged and stored in unreactive containers that preclude bacterial entry. The term "unreactive containers" implies that the container, especially its water contact surfaces, is not changed in any way by the water, such as by leaching of container-related compounds into the water or by any chemical reaction or corrosion caused by the water. The water contains no added antimicrobials and is not intended for injection. Its attributes include specifications for water conductivity, total organic carbon (or oxidizable substances), microbial limits, and bacterial endotoxins. The water conductivity and total organic carbon attributes are identical to those established for *Purified Water* and *Water for Injection*; however, instead of total organic carbon (TOC), the organic content may alternatively be measured by the test for *Oxidizable Substances*. The microbial limits attribute for this water is unique among the "bulk" water monographs, but is justified on the basis of this water's specific application that has microbial content requirements related to its safe use. The bacterial endotoxins attribute is likewise established at a level related to its safe use.

Pure Steam—*Pure Steam* (see the *USP* monograph) is also sometimes referred to as "clean steam". It is used where the steam or its condensate would directly contact official articles or article-contact surfaces, such as during their preparation, sterilization, or cleaning where no subse-

quent processing step is used to remove any codeposited impurity residues. These *Pure Steam* applications include but are not limited to porous load sterilization processes, product or cleaning solutions heated by direct steam injection, or humidification of processes where steam injection is used to control the humidity inside processing vessels where the official articles or their in-process forms are exposed. The primary intent of using this quality of steam is to ensure that official articles or article-contact surfaces exposed to it are not contaminated by residues within the steam.

Pure Steam is prepared from suitably pretreated source water analogously to either the pretreatment used for *Purified Water* or *Water for Injection*. The water is vaporized with suitable mist elimination, and distributed under pressure. The sources of undesirable contaminants within *Pure Steam* could arise from entrained source water droplets, anticorrosion steam additives, or residues from the steam production and distribution system itself. The attributes in the *Pure Steam* monograph should detect most of the contaminants that could arise from these sources. If the official article exposed to potential *Pure Steam* residues is intended for parenteral use or other applications where the pyrogenic content must be controlled, the *Pure Steam* must additionally meet the specification for the *Bacterial Endotoxins Test* (85).

These purity attributes are measured on the condensate of the article, rather than the article itself. This, of course, imparts great importance to the cleanliness of the *Pure Steam* condensate generation and collection process because it must not adversely impact the quality of the resulting condensed fluid.

Other steam attributes not detailed in the monograph, in particular, the presence of even small quantities of noncondensable gases or the existence of a superheated or dry state, may also be important for applications such as sterilization. The large release of energy (latent heat of condensation) as water changes from the gaseous to the liquid state is the key to steam's sterilization efficacy and its efficiency, in general, as a heat transfer agent. If this phase change (condensation) is not allowed to happen because the steam is extremely hot and in a persistent superheated, dry state, then its usefulness could be seriously compromised. Noncondensable gases in steam tend to stratify or collect in certain areas of a steam sterilization chamber or its load. These surfaces would thereby be at least partially insulated from the steam condensation phenomenon, preventing them from experiencing the full energy of the sterilizing conditions. Therefore, control of these kinds of steam attributes, in addition to its chemical purity, may also be important for certain *Pure Steam* applications. However, because these additional attributes are use-specific, they are not mentioned in the *Pure Steam* monograph.

Note that less pure "plant steam" may be used for steam sterilization of nonproduct contact nonporous loads, for general cleaning of nonproduct contact equipment, as a nonproduct contact heat exchange medium, and in all compatible applications involved in bulk pharmaceutical chemical and API manufacture.

Finally, owing to the lethal properties of *Pure Steam*, monitoring of microbial control within a steam system is unnecessary. Therefore, microbial analysis of the steam condensate is unnecessary.

Sterile Monographed Waters

The following monographed waters are packaged forms of either *Purified Water* or *Water for Injection* that have been sterilized to preserve their microbiological properties. These waters may have specific intended uses as indicated by their names and may also have restrictions on packaging configurations related to those uses. In general, these sterile packaged waters may be used in a variety of applications in lieu of the bulk forms of water from which they were derived. However, there is a marked contrast between the quality tests and purities for these bulk versus sterile packaged wa-

ters. These quality tests and specifications for sterile packaged waters have diverged from those of bulk waters to accommodate a wide variety of packaging types, properties, volumes, and uses. As a result, the inorganic and organic impurity specifications and levels of the bulk and sterile packaged forms of water are not equivalent as their name similarities imply. The packaging materials and elastomeric closures are the primary sources of these impurities, which tend to increase over these packaged articles' shelf lives. Therefore, due consideration must be given to the chemical purity suitability at the time of use of the sterile packaged forms of water when used in manufacturing, analytical, and cleaning applications in lieu of the bulk waters from which these waters were derived. It is the user's responsibility to ensure fitness for use of these sterile packaged waters in these applications. Nevertheless, for the applications discussed below for each sterile packaged water, their respective purities and packaging restrictions generally render them suitable by definition.

Sterile Purified Water—*Sterile Purified Water* (see the USP monograph) is *Purified Water*, packaged and rendered sterile. It is used in the preparation of nonparenteral compendial dosage forms or in analytical applications requiring *Purified Water* where access to a validated *Purified Water* system is not practical, where only a relatively small quantity is needed, where *Sterile Purified Water* is required, or where bulk packaged *Purified Water* is not suitably microbiologically controlled.

Sterile Water for Injection—*Sterile Water for Injection* (see the USP monograph) is *Water for Injection* packaged and rendered sterile. It is used for extemporaneous prescription compounding and as a sterile diluent for parenteral products. It may also be used for other applications where bulk *Water for Injection* or *Purified Water* is indicated but where access to a validated water system is either not practical or where only a relatively small quantity is needed. *Sterile Water for Injection* is packaged in single-dose containers not larger than 1 L in size.

Bacteriostatic Water for Injection—*Bacteriostatic Water for Injection* (see the USP monograph) is sterile *Water for Injection* to which has been added one or more suitable antimicrobial preservatives. It is intended to be used as a diluent in the preparation of parenteral products, most typically for multi-dose products that require repeated content withdrawals. It may be packaged in single-dose or multiple-dose containers not larger than 30 mL.

Sterile Water for Irrigation—*Sterile Water for Irrigation* (see the USP monograph) is *Water for Injection* packaged and sterilized in single-dose containers of larger than 1 L in size that allows rapid delivery of its contents. It need not meet the requirement under small-volume injections in the general test chapter *Particulate Matter in Injections* (788). It may also be used in other applications that do not have particulate matter specifications, where bulk *Water for Injection* or *Purified Water* is indicated but where access to a validated water system is not practical, or where somewhat larger quantities than are provided as *Sterile Water for Injection* are needed.

Sterile Water for Inhalation—*Sterile Water for Inhalation* (see the USP monograph) is *Water for Injection* that is packaged and rendered sterile and is intended for use in inhalators and in the preparation of inhalation solutions. It carries a less stringent specification for bacterial endotoxins than *Sterile Water for Injection* and therefore is not suitable for parenteral applications.

Nonmonographed Manufacturing Waters

In addition to the bulk monographed waters described above, nonmonographed waters can also be used in pharmaceutical processing steps such as cleaning, synthetic steps, or a starting material for further purification. The fol-

lowing is a description of several of these nonmonographed waters as cited in various locations within these compendia.

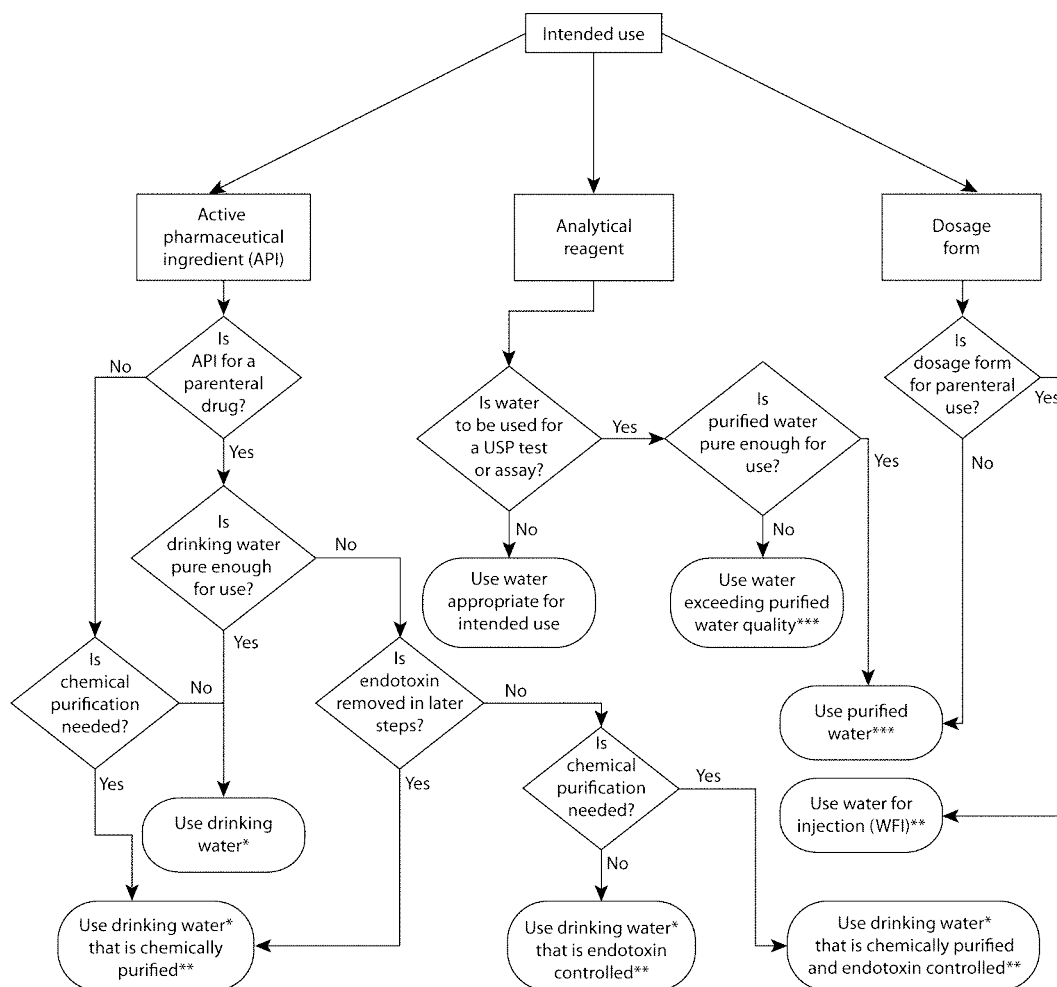
Drinking Water—This type of water can be referred to as Potable Water (meaning drinkable or fit to drink), National Primary Drinking Water, Primary Drinking Water, or National Drinking Water. Except where a singular drinking water specification is stated (such as the NPDWR [U.S. Environmental Protection Agency's National Primary Drinking Water Regulations as cited in 40 CFR Part 141]), this water must comply with the quality attributes of either the NPDWR, or the drinking water regulations of the European Union or Japan, or the WHO Drinking Water Guidelines. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of these sources. *Drinking Water* may be used in the early stages of cleaning pharmaceutical manufacturing equipment and product-contact components. *Drinking Water* is also the minimum quality of water that should be used for the preparation of official substances and other bulk pharmaceutical ingredients. Where compatible with the processes, the allowed contaminant levels in *Drinking Water* are generally considered safe for use for official substances and other drug substances. Where required by the processing of the materials to achieve their required final purity, higher qualities of water may be needed for these manufacturing steps, perhaps even as pure as *Water for Injection* or *Purified Water*. Such higher purity waters, however, might require only selected attributes to be of higher purity than *Drinking Water* (see Figure 2). *Drinking Water* is the prescribed source or feed water for the production of bulk monographed pharmaceutical waters. The use of *Drinking Water* specifications establishes a reasonable set of maximum allowable levels of chemical and microbiological contaminants with which a water purification system will be challenged. As seasonal variations in the quality attributes of the *Drinking Water* supply can occur, due consideration to its synthetic and cleaning uses must be given. The processing steps in the production of pharmaceutical waters must be designed to accommodate this variability.

Hot Purified Water—This water is used in the preparation instructions for USP–NF articles and is clearly intended to be *Purified Water* that has been heated to an unspecified temperature in order to enhance solubilization of other ingredients. There is no upper temperature limit for the water (other than being less than 100°), but for each monograph there is an implied lower limit below which the desired solubilization effect would not occur.

Nonmonographed Analytical Waters

Both *General Notices and Requirements* and the introductory section to *Reagents, Indicators, and Solutions* clearly state that where the term "water", without qualification or other specification, is indicated for use in analyses, the quality of water shall be *Purified Water*. However, numerous such qualifications do exist. Some of these qualifications involve methods of preparation, ranging from specifying the primary purification step to specifying additional purification. Other qualifications call for specific attributes to be met that might otherwise interfere with analytical processes. In most of these latter cases, the required attribute is not specifically tested. Rather, a further "purification process" is specified that ostensibly allows the water to adequately meet this required attribute.

However, preparation instructions for many reagents were carried forward from the innovator's laboratories to the originally introduced monograph for a particular USP–NF article or general test chapter. The quality of the reagent water described in these tests may reflect the water quality designation of the innovator's laboratory. These specific water designations may have originated without the innovator's awareness of the requirement for *Purified Water* in USP–NF tests. Regardless of the original reason for the creation of these numerous special analytical waters, it is possible that



* Drinking water is water complying with US EPA NPDWR or drinking water regulations of EU or Japan or WHO drinking water guidelines.

** Water for sterile APIs or dosage forms must first be rendered sterile if there is not a subsequent sterilization step in the process where used.

*** See guidance in this chapter where waters other than purified water are required by some USP tests and assays.

Note: All water systems should be validated with whatever microbial control is needed to suit the intended purposes of the water.

Figure 2. Selection of water for pharmaceutical purposes.

the attributes of these special waters could now be met by the basic preparation steps and current specifications of *Purified Water*. In some cases, however, some of the cited post-processing steps are still necessary to reliably achieve the required attributes.

Users are not obligated to employ specific and perhaps archaically generated forms of analytical water where alternatives with equal or better quality, availability, or analytical performance may exist. The consistency and reliability for producing these alternative analytical waters should be verified as producing the desired attributes. In addition, any alternative analytical water must be evaluated on an application-by-application basis by the user to ensure its suitability. Following is a summary of the various types of nonmonographed analytical waters that are cited in the *USP–NF*.

Distilled Water—This water is produced by vaporizing liquid water and condensing it in a purer state. It is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for rinsing an analyte, transferring a test material as a slurry, as a calibration standard or analytical blank, and for test apparatus cleaning. It is also cited as the starting water to be used for making *High-Purity Water*. Because none of the

cited uses of this water imply a need for a particular purity attribute that can only be derived by distillation, water meeting the requirements for *Purified Water* derived by other means of purification could be equally suitable where *Distilled Water* is specified.

Freshly Distilled Water—Also called “recently distilled water”, it is produced in a similar fashion to *Distilled Water* and should be used shortly after its generation. This implies the need to avoid endotoxin contamination as well as any other adventitious forms of contamination from the air or containers that could arise with prolonged storage. It is used for preparing solutions for subcutaneous test animal injections as well as for a reagent solvent in tests for which there appears to be no particularly high water purity needed that could be ascribable to being “freshly distilled”. In the test animal use, the term “freshly distilled” and its testing use imply a chemical, endotoxin, and microbiological purity that could be equally satisfied by *Water for Injection* (although no reference is made to these chemical, endotoxin, or microbial attributes or specific protection from recontamination). For nonanimal uses, water meeting the requirements for *Purified Water* derived by other means of purification and/or storage periods could be equally suitable where “recently distilled water” or *Freshly Distilled Water* is specified.

Deionized Water—This water is produced by an ion-exchange process in which the contaminating ions are replaced with either H^+ or OH^- ions. Similarly to *Distilled Water*, *Deionized Water* is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for transferring an analyte within a test procedure, as a calibration standard or analytical blank, and for test apparatus cleaning. Also, none of the cited uses of this water imply any needed purity attribute that can only be achieved by deionization. Therefore, water meeting the requirements for *Purified Water* that is derived by other means of purification could be equally suitable where *Deionized Water* is specified.

Freshly Deionized Water—This water is prepared in a similar fashion to *Deionized Water*, although as the name suggests, it is to be used shortly after its production. This implies the need to avoid any adventitious contamination that could occur upon storage. This water is indicated for use as a reagent solvent as well as for cleaning. Due to the nature of the testing, *Purified Water* could be a reasonable alternative for these applications.

Deionized Distilled Water—This water is produced by deionizing (see *Deionized Water*) *Distilled Water*. This water is used as a reagent in a liquid chromatography test that requires a high purity. Because of the importance of this high purity, water that barely meets the requirements for *Purified Water* may not be acceptable. *High-Purity Water* (see below) could be a reasonable alternative for this water.

Filtered Water—This water is *Purified Water* that has been filtered to remove particles that could interfere with the analysis where this water is specified. It is sometimes used synonymously with *Particle-Free Water* and *Ultra-Filtered Water* and is cited in some monographs and general chapters as well as in *Reagents*. Depending on its location, it is variously defined as water that has been passed through filters rated as 1.2- μm , 0.22- μm , or 0.2- μm ; or unspecified pore size. Although the water names and the filter pore sizes used to produce these waters are inconsistently defined, the use of 0.2- μm pore size filtered *Purified Water* should be universally acceptable for all applications where *Particle-Free Water*, *Filtered Water*, or *Ultra-Filtered Water* are specified.

High-Purity Water—This water may be prepared by deionizing previously distilled water, and then filtering it through a 0.45- μm rated membrane. This water must have an in-line conductivity of not greater than 0.15 $\mu S/cm$ (not less than 6.67 Megohm-cm) at 25°. If the water of this purity contacts the atmosphere even briefly as it is being used or drawn from its purification system, its conductivity will immediately increase, by as much as about 1.0 $\mu S/cm$, as atmospheric carbon dioxide dissolves in the water and equilibrates to hydrogen and bicarbonate ions. Therefore, if the analytical use requires that water conductivity remains as low as possible or the bicarbonate/carbon dioxide levels be as low as possible, its use should be protected from atmospheric exposure. This water is used as a reagent, as a solvent for reagent preparation, and for test apparatus cleaning where less pure waters would not perform acceptably. However, if a user's routinely available *Purified Water* is filtered and meets or exceeds the conductivity specifications of *High-Purity Water*, it could be used in lieu of *High-Purity Water*. ■ 15 (USP36)

Ammonia-Free Water—Functionally, this water must have a negligible ammonia concentration to avoid interference in tests sensitive to ammonia. It has been equated with *High-Purity Water* that has a significantly tighter *Stage 1* (see *Water Conductivity* 〈645〉) conductivity specification than *Purified Water* because of the latter's allowance for a minimal level of ammonium among other ions. However, if the user's *Purified Water* were filtered and met or exceeded the conductivity specifications of *High-Purity Water*, it would contain negligible ammonia or other ions and could be used in lieu of *High-Purity Water*.

Carbon Dioxide-Free Water—The introductory portion of the *Reagents, Indicators, and Solutions* section defines this water as *Purified Water* that has been vigorously boiled for at least 5 minutes, then cooled and protected from absorption of atmospheric carbon dioxide. Because the absorption of carbon dioxide tends to drive down the water pH, most of the uses of *Carbon Dioxide-Free Water* are either associated as a solvent in pH-related or pH-sensitive determinations or as a solvent in carbonate-sensitive reagents or determinations. Another use of this water is for certain optical rotation and color and clarity of solution tests. Although it is possible that this water is indicated for these tests simply because of its purity, it is also possible that the pH effects of carbon dioxide-containing water could interfere with the results of these tests. A third plausible reason that this water is indicated is that outgassing air bubbles might interfere with these photometric-type tests. The boiled water preparation approach will also greatly reduce the concentrations of many other dissolved gases along with carbon dioxide. Therefore, in some of the applications for *Carbon Dioxide-Free Water*, it could be the inadvertent deaeration effect that actually renders this water suitable. In addition to boiling, deionization is perhaps an even more efficient process for removing dissolved carbon dioxide (by drawing the dissolved gas equilibrium toward the ionized state with subsequent removal by the ion-exchange resins). If the starting *Purified Water* is prepared by an efficient deionization process and protected after deionization from exposure to atmospheric air, water that is carbon dioxide-free can be effectively made without the application of heat. However, this deionization process does not deaerate the water, so if *Purified Water* prepared by deionization is considered as a substitute water in a test requiring *Carbon Dioxide-Free Water*, the user must verify that it is not actually water akin to *Deaerated Water* (discussed below) that is needed for the test. As indicated in *High-Purity Water*, even brief contact with the atmosphere can allow small amounts of carbon dioxide to dissolve, ionize, and significantly degrade the conductivity and lower the pH. If the analytical use requires the water to remain as pH-neutral and as carbon dioxide-free as possible, even the analysis should be protected from atmospheric exposure. However, in most applications, atmospheric exposure during testing does not significantly affect its suitability in the test.

Ammonia- and Carbon Dioxide-Free Water—As implied by the name, this water should be prepared by approaches compatible with those mentioned for both *Ammonia-Free Water* and *Carbon Dioxide-Free Water*. Because the carbon dioxide-free attribute requires post-production protection from the atmosphere, it is appropriate to first render the water ammonia-free using the *High-Purity Water* process followed by the boiling and carbon dioxide-protected cooling process. The *High-Purity Water* deionization process for creating *Ammonia-Free Water* will also remove the ions generated from dissolved carbon dioxide and ultimately, by forced equilibration to the ionized state, all the dissolved carbon dioxide. Therefore, depending on its use, an acceptable procedure for making *Ammonia- and Carbon Dioxide-Free Water* could be to transfer and collect *High-Purity Water* in a carbon dioxide intrusion-protected container.

Deaerated Water—This water is *Purified Water* that has been treated to reduce the content of dissolved air by "suitable means". In the *Reagents* section, approaches for boiling, cooling (similar to *Carbon Dioxide-Free Water* but without the atmospheric carbon dioxide protection), and sonication are given as applicable for test uses other than dissolution and drug release testing. Although *Deaerated Water* is not mentioned by name in *Dissolution* 〈711〉, suggested methods for deaerating dissolution media (which may be water) include warming to 41°, vacuum filtering through a 0.45- μm rated membrane, and vigorously stirring the filtrate while maintaining the vacuum. This chapter specifically indicates that other validated approaches may be used. In other monographs that also do not mention *Deaer-*

ated Water by name, degassing of water and other reagents is accomplished by sparging with helium. *Deaerated Water* is used in both dissolution testing as well as liquid chromatography applications where outgassing could either interfere with the analysis itself or cause erroneous results due to inaccurate volumetric withdrawals. Applications where ambient temperature water is used for reagent preparation, but the tests are performed at elevated temperatures, are candidates for outgassing effects. If outgassing could interfere with test performance, including chromatographic flow, colorimetric or photometric measurements, or volumetric accuracy, then *Deaerated Water* should probably be used, whether called for in the analysis or not. The above deaeration approaches might not render the water “gas-free”. At best, they reduce the dissolved gas concentrations so that outgassing caused by temperature changes is not likely.

Recently Boiled Water—This water may include recently or freshly boiled water (with or without mention of cooling in the title), but cooling prior to use is clearly intended. Occasionally it is necessary to use when hot. *Recently Boiled Water* is specified because it is used in a pH-related test or carbonate-sensitive reagent, in an oxygen-sensitive test or reagent, or in a test where outgassing could interfere with the analysis, such as specific gravity or an appearance test.

Oxygen-Free Water—The preparation of this water is not specifically described in the compendia. Neither is there an oxygen specification or analysis mentioned. However, all uses involve analyses of materials that could be sensitive to oxidation by atmospheric oxygen. Procedures for the removal of dissolved oxygen from solvents, although not necessarily water, are mentioned in *Polarography* (801) and *Spectrophotometry and Light-Scattering* (851). These procedures involve simple sparging of the liquid with an inert gas such as nitrogen or helium, followed by inert gas blanketing to prevent oxygen reabsorption. The sparging times cited range from 5 to 15 minutes to an unspecified period. Some *Purified Water* and *Water for Injection* systems produce water that is maintained in a hot state and that is inert gas blanketed during its preparation and storage and distribution. Although oxygen is poorly soluble in hot water, such water may not be oxygen-free. Whatever procedure is used for removing oxygen should be verified as reliably producing water that is fit for use.

Water for BET—This water is also referred to as LAL reagent water. This is often *Water for Injection*, which may have been sterilized. It is free from a level of endotoxin that would yield any detectable reaction or interference with the *Limulus Amoebocyte Lysate* reagent used in the *Bacterial Endotoxins Test* (85).

Organic-Free Water—This water is defined by *Residual Solvents* (467) as producing no significantly interfering gas chromatography peaks. Referenced monographs specify using this water as the solvent for the preparation of standard and test solutions for the *Residual solvents* test.

Lead-Free Water—This water is used as a transferring diluent for an analyte in a *Lead* (251) test. Although no specific instructions are given for its preparation, it must not contain any detectable lead. *Purified Water* should be a suitable substitute for this water.

Chloride-Free Water—This water is specified as the solvent for use in an assay that contains a reactant that precipitates in the presence of chloride. Although no specific preparation instructions are given for this water, its rather obvious attribute is having a very low chloride level in order to be unreactive with this chloride sensitive reactant. *Purified Water* could be used for this water but should be tested to ensure that it is unreactive.

Hot Water—The uses of this water include solvents for achieving or enhancing reagent solubilization, restoring the original volume of boiled or hot solutions, rinsing insoluble analytes free of hot water soluble impurities, solvents for reagent recrystallization, apparatus cleaning, and as a solubility attribute for various USP–NF articles. In only one mon-

ograph is the temperature of “hot” water specified; so in all the other cases, the water temperature is less important, but should be high enough to achieve the desirable effect. In all cases, the chemical quality of the water is implied to be that of *Purified Water*.

VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS

Establishing the dependability of pharmaceutical water purification, storage, and distribution systems requires an appropriate period of monitoring and observation. Ordinarily, few problems are encountered in maintaining the chemical purity of *Purified Water* and *Water for Injection*. Nevertheless, the advent of using conductivity and TOC to define chemical purity has allowed the user to more quantitatively assess the water’s chemical purity and its variability as a function of routine pretreatment system maintenance and regeneration. Even the presence of such unit operations as heat exchangers and use point hoses can compromise the chemical quality of water within and delivered from an otherwise well-controlled water system. Therefore, an assessment of the consistency of the water’s chemical purity over time must be part of the validation program. However, even with the most well controlled chemical quality, it is often more difficult to consistently meet established microbiological quality criteria owing to phenomena occurring during and after chemical purification. A typical program involves intensive daily sampling and testing of major process points for at least one month after operational criteria have been established for each unit operation, point of use, and sampling point.

An overlooked aspect of water system validation is the delivery of the water to its actual location of use. If this transfer process from the distribution system outlets to the water use locations (usually with hoses) is defined as outside the water system, then this transfer process still needs to be validated to not adversely affect the quality of the water to the extent it becomes unfit for use. Because routine microbial monitoring is performed for the same transfer process and components (e.g., hoses and heat exchangers) as that of routine water use (see *Sampling Considerations*), there is some logic to including this water transfer process within the distribution system validation.

Validation is the process whereby substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes is acquired and documented. Prior to and during the very early stages of validation, the critical process parameters and their operating ranges are established. A validation program qualifies and documents the design, installation, operation, and performance of equipment. It begins when the system is defined and moves through several stages: installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). A graphical representation of a typical water system validation life cycle is shown in *Figure 3*.

A validation plan for a water system typically includes the following steps: (1) establishing standards for quality attributes of the finished water and the source water; (2) defining suitable unit operations and their operating parameters for achieving the desired finished water quality attributes from the available source water; (3) selecting piping, equipment, controls, and monitoring technologies; (4) developing an IQ stage consisting of instrument calibrations, inspections to verify that the drawings accurately depict the final configuration of the water system and, where necessary, special tests to verify that the installation meets the design requirements; (5) developing an OQ stage consisting of tests and inspections to verify that the equipment, system alerts, and controls are operating reliably and that appropriate alert and action levels are established (this phase of qualification may

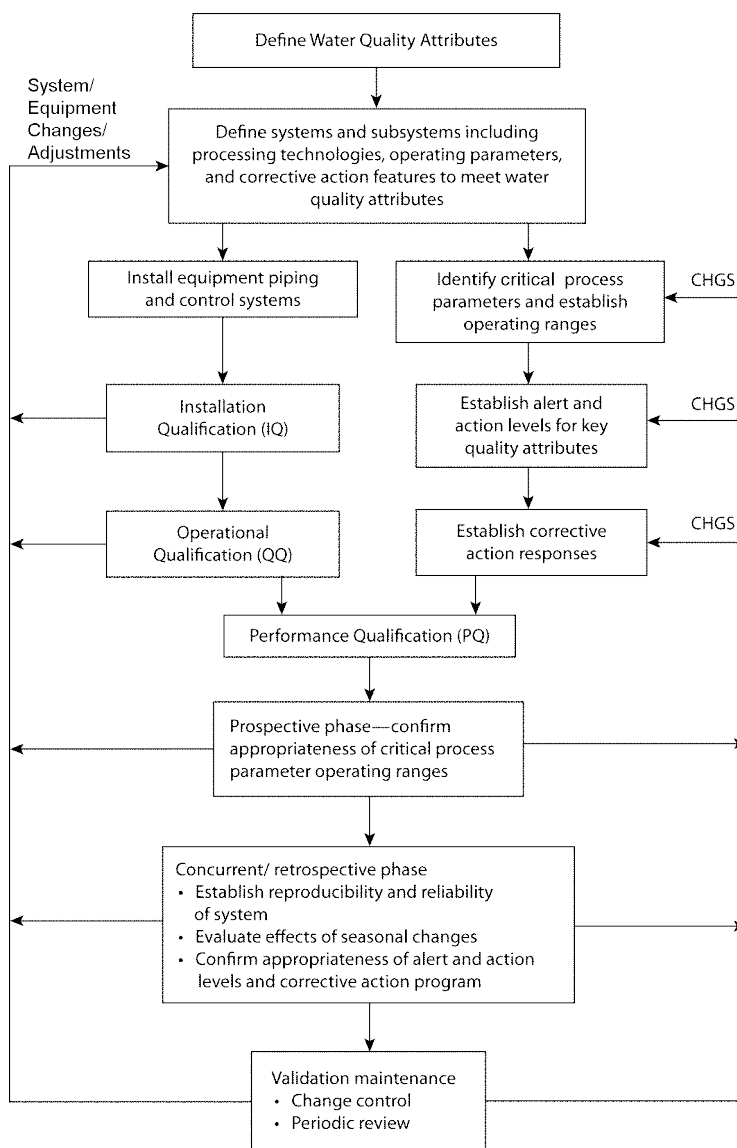


Figure 3. Water system validation life cycle.

overlap with aspects of the next step); and (6) developing a prospective PQ stage to confirm the appropriateness of critical process parameter operating ranges (during this phase of validation, alert and action levels for key quality attributes and operating parameters are verified); (7) assuring the adequacy of ongoing control procedures, e.g., sanitization frequency; (8) supplementing a validation maintenance program (also called continuous validation life cycle) that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance including recalibration of instruments (in addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program); (9) instituting a schedule for periodic review of the system performance and requalification; and (10) completing protocols and documenting Steps 1 through 9.

PURIFIED WATER AND WATER FOR INJECTION SYSTEMS

The design, installation, and operation of systems to produce *Purified Water* and *Water for Injection* include similar components, control techniques, and procedures. The qual-

ity attributes of both waters differ only in the presence of a bacterial endotoxin requirement for *Water for Injection* and in their methods of preparation, at least at the last stage of preparation. The similarities in the quality attributes provide considerable common ground in the design of water systems to meet either requirement. The critical difference is the degree of control of the system and the final purification steps needed to ensure bacterial and bacterial endotoxin removal.

Production of pharmaceutical water employs sequential unit operations (processing steps) that address specific water quality attributes and protect the operation of subsequent treatment steps. A typical evaluation process to select an appropriate water quality for a particular pharmaceutical purpose is shown in the decision tree in *Figure 2*. This diagram may be used to assist in defining requirements for specific water uses and in the selection of unit operations. The final unit operation used to produce *Water for Injection* is limited to distillation or other processes equivalent or superior to distillation in the removal of chemical impurities as well as microorganisms and their components. Distillation has a long history of reliable performance and can be validated as a unit operation for the production of *Water for Injection*, but other technologies or combinations of technol-

ogies can be validated as being equivalently effective. Other technologies, such as ultrafiltration following another chemical purification process, may be suitable in the production of *Water for Injection* if they can be shown through validation to be as effective and reliable as distillation. The advent of new materials for older technologies, such as reverse osmosis and ultrafiltration, that allow intermittent or continuous operation at elevated, microbial temperatures, show promise for a valid use in producing *Water for Injection*.

The validation plan should be designed to establish the suitability of the system and to provide a thorough understanding of the purification mechanism, range of operating conditions, required pretreatment, and the most likely modes of failure. It is also necessary to demonstrate the effectiveness of the monitoring scheme and to establish the documentation and qualification requirements for the system's validation maintenance. Trials conducted in a pilot installation can be valuable in defining the operating parameters and the expected water quality and in identifying failure modes. However, qualification of the specific unit operation can only be performed as part of the validation of the installed operational system. The selection of specific unit operations and design characteristics for a water system should take into account the quality of the feed water, the technology chosen for subsequent processing steps, the extent and complexity of the water distribution system, and the appropriate compendial requirements. For example, in the design of a system for *Water for Injection*, the final process (distillation or whatever other validated process is used according to the monograph) must have effective bacterial endotoxin reduction capability and must be validated.

UNIT OPERATIONS CONCERNS

The following is a brief description of selected unit operations and the operation and validation concerns associated with them. Not all unit operations are discussed, nor are all potential problems addressed. The purpose is to highlight issues that focus on the design, installation, operation, maintenance, and monitoring parameters that facilitate water system validation.

Prefiltration

The purpose of prefiltration—also referred to as initial, coarse, or depth filtration—is to remove solid contaminants down to a size of 7–10 μm from the incoming source water supply and protect downstream system components from particulates that can inhibit equipment performance and shorten its effective life. This coarse filtration technology utilizes primarily sieving effects for particle capture and a depth of filtration medium that has a high “dirt load” capacity. Such filtration units are available in a wide range of designs and for various applications. Removal efficiencies and capacities differ significantly, from granular bed filters such as multimedia or sand for larger water systems, to depth cartridges for smaller water systems. Unit and system configurations vary widely in type of filtering media and location in the process. Granular or cartridge prefilters are often situated at or near the head of the water pretreatment system prior to unit operations designed to remove the source water disinfectants. This location, however, does not preclude the need for periodic microbial control because biofilm can still proliferate, although at a slower rate in the presence of source water disinfectants. Design and operational issues that may impact performance of depth filters include channeling of the filtering media, blockage from silt, microbial growth, and filtering-media loss during improper backwashing. Control measures involve pressure and flow monitoring during use and backwashing, sanitizing, and replacing filtering media. An important design concern is sizing of the filter to prevent channeling or media loss resulting from inappropriate water flow rates as well as proper

sizing to minimize excessively frequent or infrequent backwashing or cartridge filter replacement.

Activated Carbon

Granular activated carbon beds adsorb low molecular weight organic material and oxidizing additives, such as chlorine and chloramine compounds, removing them from the water. They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes. The chief operating concerns regarding activated carbon beds include the propensity to support bacteria growth, the potential for hydraulic channeling, the organic adsorption capacity, appropriate water flow rates and contact time, the inability to be regenerated in situ, and the shedding of bacteria, endotoxins, organic chemicals, and fine carbon particles. Control measures may involve monitoring water flow rates and differential pressures, sanitizing with hot water or steam, backwashing, testing for adsorption capacity, and frequent replacement of the carbon bed. If the activated carbon bed is intended for organic reduction, it may also be appropriate to monitor influent and effluent TOC. It is important to note that the use of steam for carbon bed sanitization is often incompletely effective due to steam channeling rather than even permeation through the bed. This phenomenon can usually be avoided by using hot water sanitization. It is also important to note that microbial biofilm development on the surface of the granular carbon particles (as well as on other particles such as found in deionizer beds and even multimedia beds) can cause adjacent bed granules to “stick” together. When large masses of granules are agglomerated in this fashion, normal backwashing and bed fluidization flow parameters may not be sufficient to disperse them, leading to ineffective removal of trapped debris, loose biofilm, and penetration of microbial controlling conditions (as well as regenerant chemicals as in the case of agglomerated deionizer resins). Alternative technologies to activated carbon beds can be used in order to avoid their microbial problems, such as disinfectant-neutralizing chemical additives and regenerable organic scavenging devices. However, these alternatives do not function by the same mechanisms as activated carbon, may not be as effective at removing disinfectants and some organics, and have a different set of operating concerns and control measures that may be nearly as troublesome as activated carbon beds.

Additives

Chemical additives are used in water systems (a) to control microorganisms by use of sanitants such as chlorine compounds and ozone, (b) to enhance the removal of suspended solids by use of flocculating agents, (c) to remove chlorine compounds, (d) to avoid scaling on reverse osmosis membranes, and (e) to adjust pH for more effective removal of carbonate and ammonia compounds by reverse osmosis. These additives do not constitute “added substances” as long as they are either removed by subsequent processing steps or are otherwise absent from the finished water. Control of additives to ensure a continuously effective concentration and subsequent monitoring to ensure their removal should be designed into the system and included in the monitoring program.

Organic Scavengers

Organic scavenging devices use macroreticular weakly basic anion-exchange resins capable of removing organic material and endotoxins from the water. They can be regenerated with appropriate biocidal caustic brine solutions. Operating concerns are associated with organic scavenging capacity; particulate, chemical and microbiological fouling of the reactive resin surface; flow rate; regeneration fre-

quency; and shedding of resin fragments. Control measures include TOC testing of influent and effluent, backwashing, monitoring hydraulic performance, and using downstream filters to remove resin fines.

Softeners

Water softeners may be located either upstream or downstream of disinfectant removal units. They utilize sodium-based cation-exchange resins to remove water-hardness ions, such as calcium and magnesium, that could foul or interfere with the performance of downstream processing equipment such as reverse osmosis membranes, deionization devices, and distillation units. Water softeners can also be used to remove other lower affinity cations, such as the ammonium ion, that may be released from chloramine disinfectants commonly used in drinking water and which might otherwise carryover through other downstream unit operations. If ammonium removal is one of its purposes, the softener must be located downstream of the disinfectant removal operation, which itself may liberate ammonium from neutralized chloramine disinfectants. Water softener resin beds are regenerated with concentrated sodium chloride solution (brine). Concerns include microorganism proliferation, channeling caused by biofilm agglomeration of resin particles, appropriate water flow rates and contact time, ion-exchange capacity, organic and particulate resin fouling, organic leaching from new resins, fracture of the resin beads, resin degradation by excessively chlorinated water, and contamination from the brine solution used for regeneration. Control measures involve recirculation of water during periods of low water use, periodic sanitization of the resin and brine system, use of microbial control devices (e.g., UV light and chlorine), locating the unit upstream of the disinfectant removal step (if used only for softening), appropriate regeneration frequency, effluent chemical monitoring (e.g., hardness ions and possibly ammonium), and downstream filtration to remove resin fines. If a softener is used for ammonium removal from chloramine-containing source water, then capacity, contact time, resin surface fouling, pH, and regeneration frequency are very important.

Deionization

Deionization (DI), and continuous electrodeionization (CEDI) are effective methods of improving the chemical quality attributes of water by removing cations and anions. DI systems have charged resins that require periodic regeneration with an acid and base. Typically, cationic resins are regenerated with either hydrochloric or sulfuric acid, which replace the captured positive ions with hydrogen ions. Anionic resins are regenerated with sodium or potassium hydroxide, which replace captured negative ions with hydroxide ions. Because free endotoxin is negatively charged, there is some removal of endotoxin achieved by the anionic resin. Both regenerant chemicals are biocidal and offer a measure of microbial control. The system can be designed so that the cation and anion resins are in separate or “twin” beds or they can be mixed together to form a mixed bed. Twin beds are easily regenerated but deionize water less efficiently than mixed beds, which have a considerably more complex regeneration process. Rechargeable resin canisters can also be used for this purpose.

The CEDI system uses a combination of mixed resin, selectively permeable membranes, and an electric charge, providing continuous flow (product and waste concentrate) and continuous regeneration. Water enters both the resin section and the waste (concentrate) section. As it passes through the resin, it is deionized to become product water. The resin acts as a conductor enabling the electrical potential to drive the captured cations and anions through the resin and appropriate membranes for concentration and removal in the waste water stream. The electrical potential also separates the water in the resin (product) section into

hydrogen and hydroxide ions. This permits continuous regeneration of the resin without the need for regenerant additives. However, unlike conventional deionization, CEDI units must start with water that is already partially purified because they generally cannot produce *Purified Water* quality when starting with the heavier ion load of unpurified source water.

Concerns for all forms of deionization units include microbial and endotoxin control, chemical additive impact on resins and membranes, and loss, degradation, and fouling of resin. Issues of concern specific to DI units include regeneration frequency and completeness, channeling caused by biofilm agglomeration of resin particles, organic leaching from new resins, complete resin separation for mixed bed regeneration, and mixing air contamination (mixed beds). Control measures vary but typically include recirculation loops, effluent microbial control by UV light, conductivity monitoring, resin testing, microporous filtration of mixing air, microbial monitoring, frequent regeneration to minimize and control microorganism growth, sizing the equipment for suitable water flow and contact time, and use of elevated temperatures. Internal distributor and regeneration piping for mixed bed units should be configured to ensure that regeneration chemicals contact all internal bed and piping surfaces and resins. Rechargeable canisters can be the source of contamination and should be carefully monitored. Full knowledge of previous resin use, minimum storage time between regeneration and use, and appropriate sanitizing procedures are critical factors ensuring proper performance.

Reverse Osmosis

Reverse osmosis (RO) units employ semipermeable membranes. The “pores” of RO membranes are actually intersegmental spaces among the polymer molecules. They are big enough for permeation of water molecules, but too small to permit passage of hydrated chemical ions. However, many factors including pH, temperature, and differential pressure across the membrane affect the selectivity of this permeation. With the proper controls, RO membranes can achieve chemical, microbial, and endotoxin quality improvement. The process streams consist of supply water, product water (permeate), and wastewater (reject). Depending on source water, pretreatment and system configuration variations and chemical additives may be necessary to achieve desired performance and reliability.

A major factor affecting RO performance is the permeate recovery rate, that is, the amount of the water passing through the membrane compared to the amount rejected. This is influenced by the several factors, but most significantly by the pump pressure. Recoveries of 75% are typical, and can accomplish a 1–2 log purification of most impurities. For most feed waters, this is usually not enough to meet *Purified Water* conductivity specifications. A second pass of this permeate water through another RO stage usually achieves the necessary permeate purity if other factors such as pH and temperature have been appropriately adjusted and the ammonia from chloraminated source water has been previously removed. Increasing recoveries with higher pressures in order to reduce the volume of reject water will lead to reduced permeate purity. If increased pressures are needed over time to achieve the same permeate flow, this is an indication of partial membrane blockage that needs to be corrected before it becomes irreversibly fouled, and expensive membrane replacement is the only option.

Other concerns associated with the design and operation of RO units include membrane materials that are extremely sensitive to sanitizing agents and to particulate, chemical, and microbial membrane fouling; membrane and seal integrity; the passage of dissolved gases, such as carbon dioxide and ammonia; and the volume of wastewater, particularly where water discharge is tightly regulated by local authorities. Failure of membrane or seal integrity will result in prod-

uct water contamination. Methods of control involve suitable pretreatment of the influent water stream, appropriate membrane material selection, integrity challenges, membrane design and heat tolerance, periodic sanitization, and monitoring of differential pressures, conductivity, microbial levels, and TOC.

The development of RO units that can tolerate sanitizing water temperatures as well as operate efficiently and continuously at elevated temperatures has added greatly to their microbial control and to the avoidance of biofouling. RO units can be used alone or in combination with DI and CEDI units as well as ultrafiltration for operational and quality enhancements.

Ultrafiltration

Ultrafiltration is a technology most often employed in pharmaceutical water systems for removing endotoxins from a water stream. It can also use semipermeable membranes, but unlike RO, these typically use polysulfone membranes whose intersegmental “pores” have been purposefully exaggerated during their manufacture by preventing the polymer molecules from reaching their smaller equilibrium proximities to each other. Depending on the level of equilibrium control during their fabrication, membranes with differing molecular weight “cutoffs” can be created such that molecules with molecular weights above these cutoff ratings are rejected and cannot penetrate the filtration matrix.

Ceramic ultrafilters are another molecular sieving technology. Ceramic ultrafilters are self supporting and extremely durable, backwashable, chemically cleanable, and steam sterilizable. However, they may require higher operating pressures than membrane type ultrafilters.

All ultrafiltration devices work primarily by a molecular sieving principle. Ultrafilters with molecular weight cutoff ratings in the range of 10,000–20,000 Da are typically used in water systems for removing endotoxins. This technology may be appropriate as an intermediate or final purification step. Similar to RO, successful performance is dependent upon pretreatment of the water by upstream unit operations.

Issues of concern for ultrafilters include compatibility of membrane material with heat and sanitizing agents, membrane integrity, fouling by particles and microorganisms, and seal integrity. Control measures involve filtration medium selection, sanitization, flow design (dead end vs. tangential), integrity challenges, regular cartridge changes, elevated feed water temperature, and monitoring TOC and differential pressure. Additional flexibility in operation is possible based on the way ultrafiltration units are arranged such as in a parallel or series configurations. Care should be taken to avoid stagnant water conditions that could promote microorganism growth in back-up or standby units.

Charge-Modified Filtration

Charge-modified filters are usually microbially retentive filters that are treated during their manufacture to have a positive charge on their surfaces. Microbial-retentive filtration will be described in a subsequent section, but the significant feature of these membranes is their electrostatic surface charge. Such charged filters can reduce endotoxin levels in the fluids passing through them by their adsorption (owing to the endotoxin's negative charge) onto the membrane surfaces. Although ultrafilters are more often employed as a unit operation for endotoxin removal in water systems, charge-modified filters may also have a place in endotoxin removal particularly where available upstream pressures are not sufficient for ultrafiltration and for a single, relatively short-term use. Charge-modified filters may be difficult to validate for long-term or large-volume endotoxin retention. Even though their purified standard endotoxin retention can be well characterized, their retention capacity for “natural” endotoxins is difficult to gauge. Nevertheless, utility could

be demonstrated and validated as short-term, single-use filters at points of use in water systems that are not designed for endotoxin control or where only an endotoxin “polishing” (removal of only slight or occasional endotoxin levels) is needed. Control and validation concerns include volume and duration of use, flow rate, water conductivity and purity, and constancy and concentration of endotoxin levels being removed. All of these factors may have to be evaluated and challenged prior to using this approach, making this a difficult-to-validate application. Even so, there may still be a possible need for additional backup endotoxin testing both upstream and downstream of the filter.

Microbial-Retentive Filtration

Microbial-retentive membrane filters have experienced an evolution of understanding in the past decade that has caused previously held theoretical retention mechanisms to be reconsidered. These filters have a larger effective “pore size” than ultrafilters and are intended to prevent the passage of microorganisms and similarly sized particles without unduly restricting flow. This type of filtration is widely employed within water systems for filtering the bacteria out of both water and compressed gases as well as for vent filters on tanks and stills and other unit operations. However, the properties of the water system microorganisms seem to challenge a filter's microbial retention from water with phenomena absent from other aseptic filtration applications, such as filter sterilizing of pharmaceutical formulations prior to packaging. In the latter application, sterilizing grade filters are generally considered to have an assigned rating of 0.2 or 0.22 μm . This rather arbitrary rating is associated with filters that have the ability to retain a high level challenge of a specially prepared inoculum of *Brevundimonas* (formerly *Pseudomonas*) *diminuta*. This is a small microorganism originally isolated decades ago from a product that had been “filter sterilized” using a 0.45- μm rated filter. Further study revealed that a percentage of cells of this microorganism could reproducibly penetrate the 0.45- μm sterilizing filters. Through historic correlation of *B. diminuta*-retaining tighter filters, thought to be twice as good as a 0.45- μm filter, assigned ratings of 0.2 or 0.22 μm with their successful use in product solution filter sterilization, both this filter rating and the associated high level *B. diminuta* challenge have become the current benchmarks for sterilizing filtration. New evidence now suggests that for microbial-retentive filters used for pharmaceutical water, *B. diminuta* may not be the best model microorganism.

An archaic understanding of microbial-retentive filtration would lead one to equate a filter's rating with the false impression of a simple sieve or screen that absolutely retains particles sized at or above the filter's rating. A current understanding of the mechanisms involved in microbial retention and the variables that can affect those mechanisms has yielded a far more complex interaction of phenomena than previously understood. A combination of simple sieve retention and surface adsorption are now known to contribute to microbial retention.

The following all interact to create some unusual and surprising retention phenomena for water system microorganisms: the variability in the range and average pore sizes created by the various membrane fabrication processes, the variability of the surface chemistry and three-dimensional structures related to the different polymers used in these filter matrices, and the size and surface properties of the microorganism intended to be retained by the filters. *B. diminuta* may not be the best challenge microorganisms for demonstrating bacterial retention for 0.2- to 0.22- μm rated filters for use in water systems because it appears to be more easily retained by these filters than some water system flora. The well-documented appearance of water system microorganisms on the downstream sides of some 0.2- to 0.22- μm rated filters after a relatively short period of use seems to support that some penetration phenomena are at

work. Unknown for certain is if this downstream appearance is caused by a “blow-through” or some other pass-through phenomenon as a result of tiny cells or less cell “stickiness”, or by a “growth through” phenomenon as a result of cells hypothetically replicating their way through the pores to the downstream side. Whatever is the penetration mechanism, 0.2- to 0.22- μm rated membranes may not be the best choice for some water system uses.

Microbial retention success in water systems has been reported with the use of some manufacturers’ filters arbitrarily rated as 0.1 μm . There is general agreement that for a given manufacturer, their 0.1- μm rated filters are tighter than their 0.2- to 0.22- μm rated filters. However, comparably rated filters from different manufacturers in water filtration applications may not perform equivalently owing to the different filter fabrication processes and the nonstandardized microbial retention challenge processes currently used for defining the 0.1- μm filter rating. It should be noted that use of 0.1- μm rated membranes generally results in a sacrifice in flow rate compared to 0.2- to 0.22- μm membranes, so whatever membranes are chosen for a water system application, the user must verify that the membranes are suitable for their intended application, use period, and use process, including flow rate.

For microbial retentive gas filtrations, the same sieving and adsorptive retention phenomena are at work as in liquid filtration, but the adsorptive phenomenon is enhanced by additional electrostatic interactions between particles and filter matrix. These electrostatic interactions are so strong that particle retention for a given filter rating is significantly more efficient in gas filtration than in water or product solution filtrations. These additional adsorptive interactions render filters rated at 0.2–0.22 μm unquestionably suitable for microbial retentive gas filtrations. When microbially retentive filters are used in these applications, the membrane surface is typically hydrophobic (non-wettable by water). A significant area of concern for gas filtration is blockage of tank vents by condensed water vapor, which can cause mechanical damage to the tank. Control measures include electrical or steam tracing and a self-draining orientation of vent filter housings to prevent accumulation of vapor condensate. However, a continuously high filter temperature will take an oxidative toll on polypropylene components of the filter, so sterilization of the unit prior to initial use, and periodically thereafter, as well as regular visual inspections, integrity tests, and changes are recommended control methods.

In water applications, microbial-retentive filters may be used downstream of unit operations that tend to release microorganisms or upstream of unit operations that are sensitive to microorganisms. Microbial-retentive filters may also be used to filter water feeding the distribution system. It should be noted that regulatory authorities allow the use of microbial-retentive filters within distribution systems or even at use points if they have been properly validated and are appropriately maintained. A point-of-use filter should only be intended to “polish” the microbial quality of an otherwise well-maintained system and not to serve as the primary microbial control device. The efficacy of system microbial control measures can only be assessed by sampling the water upstream of the filters. As an added measure of protection, in-line UV lamps, appropriately sized for the flow rate (see *Sanitization*), may be used just upstream of microbial-retentive filters to inactivate microorganisms prior to their capture by the filter. This tandem approach tends to greatly delay potential microbial penetration phenomena and can substantially extend filter service life.

Ultraviolet Light

The use of low-pressure UV lights that emit a 254-nm wavelength for microbial control is discussed under *Sanitization*, but the application of UV light in chemical purification is also emerging. This 254-nm wavelength is also useful in

the destruction of ozone. With intense emissions at wavelengths around 185 nm (as well as at 254 nm), medium pressure UV lights have demonstrated utility in the destruction of the chlorine-containing disinfectants used in source water as well as for interim stages of water pretreatment. High intensities of this wavelength alone or in combination with other oxidizing sanitants, such as hydrogen peroxide, have been used to lower TOC levels in recirculating distribution systems. The organics are typically converted to carbon dioxide, which equilibrates to bicarbonate, and incompletely oxidized carboxylic acids, both of which can easily be removed by polishing ion-exchange resins. Areas of concern include adequate UV intensity and residence time, gradual loss of UV emissivity with bulb age, gradual formation of UV-absorbing film at the water contact surface, incomplete photodegradation during unforeseen source water hyperchlorination, release of ammonia from chloramine photodegradation, unapparent UV bulb failure, and conductivity degradation in distribution systems using 185-nm UV lights. Control measures include regular inspection or emissivity alarms to detect bulb failures or film occlusions, regular UV bulb sleeve cleaning and wiping, downstream chlorine detectors, downstream polishing deionizers, and regular (approximately yearly) bulb replacement.

Distillation

Distillation units provide chemical and microbial purification via thermal vaporization, mist elimination, and water vapor condensation. A variety of designs is available including single effect, multiple effect, and vapor compression. The latter two configurations are normally used in larger systems because of their generating capacity and efficiency. Distilled water systems require different feed water controls than required by membrane systems. For distillation, due consideration must be given to prior removal of hardness and silica impurities that may foul or corrode the heat transfer surfaces as well as prior removal of those impurities that could volatilize and condense along with the water vapor. In spite of general perceptions, even the best distillation process cannot afford absolute removal of contaminating ions and endotoxin. Most stills are recognized as being able to accomplish at least a 3–4 log reduction in these impurity concentrations. Areas of concern include carry-over of volatile organic impurities such as trihalomethanes (see *Source or Feed Water Considerations*) and gaseous impurities such as ammonia and carbon dioxide, faulty mist elimination, evaporator flooding, inadequate blowdown, stagnant water in condensers and evaporators, pump and compressor seal design, pinhole evaporator and condenser leaks, and conductivity (quality) variations during start-up and operation.

Methods of control may involve preliminary decarbonation steps to remove both dissolved carbon dioxide and other volatile or noncondensable impurities; reliable mist elimination to minimize feedwater droplet entrainment; visual or automated high water level indication to detect boiler flooding and boil over; use of sanitary pumps and compressors to minimize microbial and lubricant contamination of feedwater and condensate; proper drainage during inactive periods to minimize microbial growth and accumulation of associated endotoxin in boiler water; blowdown control to limit the impurity concentration effect in the boiler to manageable levels; on-line conductivity sensing with automated diversion to waste to prevent unacceptable water upon still startup or still malfunction from getting into the finished water distribute system; and periodic integrity testing for pinhole leaks to routinely assure condensate is not compromised by nonvolatilized source water contaminants.

Storage Tanks

Storage tanks are included in water distribution systems to optimize processing equipment capacity. Storage also allows for routine maintenance within the pretreatment train

while maintaining continuous supply to meet manufacturing needs. Design and operation considerations are needed to prevent or minimize the development of biofilm, to minimize corrosion, to aid in the use of chemical sanitization of the tanks, and to safeguard mechanical integrity. These considerations may include using closed tanks with smooth interiors, the ability to spray the tank headspace using sprayballs on recirculating loop returns, and the use of heated, jacketed/insulated tanks. This minimizes corrosion and biofilm development and aids in thermal and chemical sanitization. Storage tanks require venting to compensate for the dynamics of changing water levels. This can be accomplished with a properly oriented and heat-traced filter housing fitted with a hydrophobic microbial retentive membrane filter affixed to an atmospheric vent. Alternatively, an automatic membrane-filtered compressed gas blanketing system may be used. In both cases, rupture disks equipped with a rupture alarm device should be used as a further safeguard for the mechanical integrity of the tank. Areas of concern include microbial growth or corrosion due to irregular or incomplete sanitization and microbial contamination from unalarmed rupture disk failures caused by condensate-occluded vent filters.

Distribution Systems

Distribution system configuration should allow for the continuous flow of water in the piping by means of recirculation. Use of nonrecirculating, dead-end, or one-way systems or system segments should be avoided whenever possible. If not possible, these systems should be periodically flushed and more closely monitored. Experience has shown that continuously recirculated systems are easier to maintain. Pumps should be designed to deliver fully turbulent flow conditions to facilitate thorough heat distribution (for hot water sanitized systems) as well as thorough chemical sanitant distribution. Turbulent flow also appear to either retard the development of biofilms or reduce the tendency of those biofilms to shed bacteria into the water. If redundant pumps are used, they should be configured and used to avoid microbial contamination of the system.

Components and distribution lines should be sloped and fitted with drain points so that the system can be completely drained. In stainless steel distribution systems where the water is circulated at a high temperature, dead legs and low-flow conditions should be avoided, and valved tie-in points should have length-to-diameter ratios of six or less. If constructed of heat-tolerant plastic, this ratio should be even less to avoid cool points where biofilm development could occur. In ambient temperature distribution systems, particular care should be exercised to avoid or minimize dead leg ratios of any size and provide for complete drainage. If the system is intended to be steam sanitized, careful sloping and low-point drainage is crucial to condensate removal and sanitization success. If drainage of components or distribution lines is intended as a microbial control strategy, they should also be configured to be completely dried using dry compressed air (or nitrogen if appropriate employee safety measures are used). Drained but still moist surfaces will still support microbial proliferation. Water exiting from the distribution system should not be returned to the system without first passing through all or a portion of the purification train.

The distribution design should include the placement of sampling valves in the storage tank and at other locations, such as in the return line of the recirculating water system. Where feasible, the primary sampling sites for water should be the valves that deliver water to the points of use. Direct connections to processes or auxiliary equipment should be designed to prevent reverse flow into the controlled water system. Hoses and heat exchangers that are attached to points of use in order to deliver water for a particular use must not chemically or microbiologically degrade the water quality. The distribution system should permit sanitization

for microorganism control. The system may be continuously operated at sanitizing conditions or sanitized periodically.

INSTALLATION, MATERIALS OF CONSTRUCTION, AND COMPONENT SELECTION

Installation techniques are important because they can affect the mechanical, corrosive, and sanitary integrity of the system. Valve installation attitude should promote gravity drainage. Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst-case thermal and flow conditions. The methods of connecting system components including units of operation, tanks, and distribution piping require careful attention to preclude potential problems. Stainless steel welds should provide reliable joints that are internally smooth and corrosion-free. Low-carbon stainless steel, compatible wire filler, where necessary, inert gas, automatic welding machines, and regular inspection and documentation help to ensure acceptable weld quality. Follow-up cleaning and passivation are important for removing contamination and corrosion products and to re-establish the passive corrosion-resistant surface. Plastic materials can be fused (welded) in some cases and also require smooth, uniform internal surfaces. Adhesive glues and solvents should be avoided due to the potential for voids and extractables. Mechanical methods of joining, such as flange fittings, require care to avoid the creation of offsets, gaps, penetrations, and voids. Control measures include good alignment, properly sized gaskets, appropriate spacing, uniform sealing force, and the avoidance of threaded fittings.

Materials of construction should be selected to be compatible with control measures such as sanitizing, cleaning, and passivating. Temperature rating is a critical factor in choosing appropriate materials because surfaces may be required to handle elevated operating and sanitization temperatures. Should chemicals or additives be used to clean, control, or sanitize the system, materials resistant to these chemicals or additives must be utilized. Materials should be capable of handling turbulent flow and elevated velocities without wear of the corrosion-resistant film such as the passive chromium oxide surface of stainless steel. The finish on metallic materials such as stainless steel, whether it is a refined mill finish, polished to a specific grit, or an electropolished treatment, should complement system design and provide satisfactory corrosion and microbial activity resistance as well as chemical sanitizability. Auxiliary equipment and fittings that require seals, gaskets, diaphragms, filter media, and membranes should exclude materials that permit the possibility of extractables, shedding, and microbial activity. Insulating materials exposed to stainless steel surfaces should be free of chlorides to avoid the phenomenon of stress corrosion cracking that can lead to system contamination and the destruction of tanks and critical system components.

Specifications are important to ensure proper selection of materials and to serve as a reference for system qualification and maintenance. Information such as mill reports for stainless steel and reports of composition, ratings, and material handling capabilities for nonmetallic substances should be reviewed for suitability and retained for reference. Component (auxiliary equipment) selection should be made with assurance that it does not create a source of contamination intrusion. Heat exchangers should be constructed to prevent leakage of heat transfer medium to the pharmaceutical water and, for heat exchanger designs where prevention may fail, there should be a means to detect leakage. Pumps should be of sanitary design with seals that prevent contamination of the water. Valves should have smooth internal surfaces with the seat and closing device exposed to the flushing action of water, such as occurs in diaphragm valves. Valves with pocket areas or closing devices (e.g., ball, plug,

gate, globe) that move into and out of the flow area should be avoided.

SANITIZATION

Microbial control in water systems is achieved primarily through sanitization practices. Systems can be sanitized using either thermal or chemical means. Thermal approaches to system sanitization include periodic or continuously circulating hot water and the use of steam. Temperatures of at least 80° are most commonly used for this purpose, but continuously recirculating water of at least 65° has also been used effectively in insulated stainless steel distribution systems when attention is paid to uniformity and distribution of such self-sanitizing temperatures. These techniques are limited to systems that are compatible with the higher temperatures needed to achieve sanitization. Although thermal methods control biofilm development by either continuously inhibiting their growth or, in intermittent applications, by killing the microorganisms within biofilms, they are not effective in removing established biofilms. Killed but intact biofilms can become a nutrient source for rapid biofilm regrowth after the sanitizing conditions are removed or halted. In such cases, a combination of routine thermal and periodic supplementation with chemical sanitization might be more effective. The more frequent the thermal sanitization, the more likely biofilm development and regrowth can be eliminated. Chemical methods, where compatible, can be used on a wider variety of construction materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, peracetic acid, or combinations thereof. Halogenated compounds are effective sanitizers but are difficult to flush from the system and may leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radicals (notably hydroxyl radicals). The short half-life of ozone in particular, and its limitation on achievable concentrations require that it be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of UV light. In fact, ozone's ease of degradation to oxygen using 254-nm UV light at use points allow it to be most effectively used on a continuous basis to provide continuously sanitizing conditions.

In-line UV light at a wavelength of 254 nm can also be used to continuously "sanitize" water circulating in the system, but these devices must be properly sized for the water flow. Such devices inactivate a high percentage (but not 100%) of microorganisms that flow through the device but cannot be used to directly control existing biofilm upstream or downstream of the device. However, when coupled with conventional thermal or chemical sanitization technologies or located immediately upstream of a microbially retentive filter, it is most effective and can prolong the interval between system sanitizations.

It is important to note that microorganisms in a well-developed biofilm can be extremely difficult to kill, even by aggressive oxidizing biocides. The less developed and therefore thinner the biofilm, the more effective the biocidal action. Therefore, optimal biocide control is achieved by frequent biocide use that does not allow significant biofilm development between treatments.

Sanitization steps require validation to demonstrate the capability of reducing and holding microbial contamination at acceptable levels. Validation of thermal methods should include a heat distribution study to demonstrate that sanitization temperatures are achieved throughout the system, including the body of use point valves. Validation of chemical methods requires demonstrating adequate chemical concentrations throughout the system, exposure to all wetted surfaces, including the body of use-point valves, and complete removal of the sanitant from the system at the completion of treatment. Methods validation for the detection

and quantification of residues of the sanitant or its objectionable degradants is an essential part of the validation program. The frequency of sanitization should be supported by, if not triggered by, the results of system microbial monitoring. Conclusions derived from trend analysis of the microbiological data should be used as the alert mechanism for maintenance. The frequency of sanitization should be established in such a way that the system operates in a state of microbiological control and does not routinely exceed alert levels (see *Alert and Action Levels and Specifications*).

OPERATION, MAINTENANCE, AND CONTROL

A preventive maintenance program should be established to ensure that the water system remains in a state of control. The program should include (1) procedures for operating the system, (2) monitoring programs for critical quality attributes and operating conditions including calibration of critical instruments, (3) schedule for periodic sanitization, (4) preventive maintenance of components, and (5) control of changes to the mechanical system and to operating conditions.

Operating Procedures—Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also define the point when action is required. The procedures should be well documented, detail the function of each job, assign who is responsible for performing the work, and describe how the job is to be conducted. The effectiveness of these procedures should be assessed during water system validation.

Monitoring Program—Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or automated instruments (e.g., for TOC, conductivity, hardness, and chlorine), automated or manual documentation of operational parameters (such as flow rates or pressure drop across a carbon bed, filter, or RO unit), and laboratory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the necessity for initiating corrective action should be included.

Sanitization—Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of microbial control. Technologies for sanitization are described above.

Preventive Maintenance—A preventive maintenance program should be in effect. The program should establish what preventive maintenance is to be performed, the frequency of maintenance work, and how the work should be documented.

Change Control—The mechanical configuration and operating conditions must be controlled. Proposed changes should be evaluated for their impact on the whole system. The need to requalify the system after changes are made should be determined. Following a decision to modify a water system, the affected drawings, manuals, and procedures should be revised.

SAMPLING CONSIDERATIONS

Water systems should be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality. Samples should be taken from representative locations within the processing and distribution system. Established sampling frequencies should be based on system validation data and should cover critical areas including unit operation sites. The sampling plan should take into consideration the desired attributes of the water being sampled. For example, systems for *Water for Injection*, because of their more critical microbiological re-

quirements, may require a more rigorous sampling frequency.

Analyses of water samples often serve two purposes: in-process control assessments and final quality control assessments. In-process control analyses are usually focused on the attributes of the water within the system. Quality control is primarily concerned with the attributes of the water delivered by the system to its various uses. The latter usually employs some sort of transfer device, often a flexible hose, to bridge the gap between the distribution system use-point valve and the actual location of water use. The issue of sample collection location and sampling procedure is often hotly debated because of the typically mixed use of the data generated from the samples, for both in-process control and quality control. In these single-sample and mixed-data use situations, the worst-case scenario should be utilized. In other words, samples should be collected from use points using the same delivery devices, such as hoses, and procedures, such as preliminary hose or outlet flushing, as are employed by production from those use points. Where use points per se cannot be sampled, such as hard-piped connections to equipment, special sampling ports may be used. In all cases, the sample must represent as closely as possible the quality of the water used in production. If a point-of-use filter is employed, sampling of the water prior to and after the filter is needed, because the filter will mask the microbial control achieved by the normal operating procedures of the system.

Samples containing chemical sanitizing agents require neutralization prior to microbiological analysis. Samples for microbiological analysis should be tested immediately, or suitably refrigerated to preserve the original microbial attributes until analysis can begin. Samples of flowing water are only indicative of the concentration of planktonic (free floating) microorganisms present in the system. Biofilm microorganisms (those attached to water system surfaces) are usually present in greater numbers and are the source of the planktonic population recovered from grab samples. Microorganisms in biofilms represent a continuous source of contamination and are difficult to directly sample and quantify. Consequently, the planktonic population is usually used as an indicator of system contamination levels and is the basis for system *Alert and Action Levels and Specifications*. The consistent appearance of elevated planktonic levels is usually an indication of advanced biofilm development in need of remedial control. System control and sanitization are key in controlling biofilm formation and the consequent planktonic population.

Sampling for chemical analyses is also done for in-process control and for quality control purposes. However, unlike microbial analyses, chemical analyses can be and often are performed using on-line instrumentation. Such on-line testing has unequivocal in-process control purposes because it is not performed on the water delivered from the system. However, unlike microbial attributes, chemical attributes are usually not significantly degraded by hoses. Therefore, through verification testing, it may be possible to show that the chemical attributes detected by the on-line instrumentation (in-process testing) are equivalent to those detected at the ends of the use-point hoses (quality control testing). This again creates a single-sample and mixed-data use scenario. It is far better to operate the instrumentation in a continuous mode, generating large volumes of in-process data, but only using a defined small sampling of that data for QC purposes. Examples of acceptable approaches include using highest values for a given period, highest time-weighted average for a given period (from fixed or rolling sub-periods), or values at a fixed daily time. Each approach has advantages and disadvantages relative to calculation complexity and reflection of continuous quality, so the user must decide which approach is most suitable or justifiable.

Change to read:

CHEMICAL CONSIDERATIONS

The chemical attributes of *Purified Water* and *Water for Injection* in effect prior to USP 23 were specified by a series of chemistry tests for various specific and nonspecific attributes with the intent of detecting chemical species indicative of incomplete or inadequate purification. While these methods could have been considered barely adequate to control the quality of these waters, they nevertheless stood the test of time. This was partly because the operation of water systems was, and still is, based on on-line conductivity measurements and specifications generally thought to preclude the failure of these archaic chemistry attribute tests.

USP moved away from these chemical attribute tests to contemporary analytical technologies for the bulk waters *Purified Water* and *Water for Injection*. The intent was to upgrade the analytical technologies without tightening the quality requirements. The two contemporary analytical technologies employed were TOC and conductivity. The TOC test replaced the test for *Oxidizable Substances* that primarily targeted organic contaminants. A multistaged *Conductivity* test which detects ionic (mostly inorganic) contaminants replaced, with the exception of the test for *Heavy metals*, all of the inorganic chemical tests (i.e., *Ammonia*, *Calcium*, *Carbon dioxide*, *Chloride*, *Sulfate*).

Replacing the heavy metals attribute was considered unnecessary because (a) the source water specifications (found in the NPDWR) for individual *Heavy metals* were tighter than the approximate limit of detection of the *Heavy metals* test for USP XXII *Water for Injection* and *Purified Water* (approximately 0.1 ppm), (b) contemporary water system construction materials do not leach heavy metal contaminants, and (c) test results for this attribute have uniformly been negative—there has not been a confirmed occurrence of a singular test failure (failure of only the *Heavy metals* test with all other attributes passing) since the current heavy metal drinking water standards have been in place. Nevertheless, because the presence of heavy metals in *Purified Water* or *Water for Injection* could have dire consequences, its absence should at least be documented during new water system commissioning and validation or through prior test results records.

Total solids and *pH* were the only tests not covered by conductivity testing. The test for *Total solids* was considered redundant because the nonselective tests of conductivity and TOC could detect most chemical species other than silica, which could remain undetected in its colloidal form. Colloidal silica in *Purified Water* and *Water for Injection* is easily removed by most water pretreatment steps and even if present in the water, constitutes no medical or functional hazard except under extreme and rare situations. In such extreme situations, other attribute extremes are also likely to be detected. It is, however, the user's responsibility to ensure fitness for use. If silica is a significant component in the source water, and the purification unit operations could be operated or fail and selectively allow silica to be released into the finished water (in the absence of co-contaminants detectable by conductivity), then either silica-specific or a total solids type testing should be utilized to monitor and control this rare problem.

The *pH* attribute was eventually recognized to be redundant to the conductivity test (which included *pH* as an aspect of the test and specification); therefore, *pH* was dropped as a separate attribute test.

The rationale used by USP to establish its *Purified Water* and *Water for Injection* conductivity specifications took into consideration the conductivity contributed by the two least conductive former attributes of *Chloride* and *Ammonia*, thereby precluding their failure had those wet chemistry tests been performed. In essence, the *Stage 3* conductivity specifications (see *Water Conductivity* (645), *Bulk Water*) were

established from the sum of the conductivities of the limit concentrations of chloride ions (from pH 5.0–6.2) and ammonia ions (from pH 6.3–7.0), plus the unavoidable contribution of other conductivity-contributing ions from water (H^+ and OH^-), dissolved atmospheric CO_2 (as HCO_3^-), and an electro-balancing quantity of either Na^+ or Cl^- , depending on the pH-induced ionic imbalance (see *Table 1*). The *Stage 2* conductivity specification is the lowest value on this table, 2.1 $\mu S/cm$. The *Stage 1* specifications, designed primarily for on-line measurements, were derived essentially by summing the lowest values in the contributing ion columns for each of a series of tables similar to *Table 1*, created for each 5° increment between 0° and 100°. For example purposes, the italicized values in *Table 1*, the conductivity data table for 25°, were summed to yield a conservative value of 1.3 $\mu S/cm$, the *Stage 1* specification for a nontemperature compensated, nonatmosphere equilibrated water sample that actually had a measured temperature of 25°–29°. Each 5° increment in the table was similarly treated to yield the individual values listed in the table of *Stage 1* specifications (see *Water Conductivity* 〈645〉, *Bulk Water*).

As stated above, this rather radical change to utilizing a conductivity attribute as well as the inclusion of a TOC attribute allowed for on-line measurements. This was a major philosophical change and allowed major savings to be realized by industry. The TOC and conductivity tests can also be performed “off-line” in the laboratories using collected samples, although sample collection tends to introduce opportunities for adventitious contamination that can cause false high readings. The collection of on-line data is not, however, without challenges. The continuous readings tend to create voluminous amounts of data where before only a single data point was available. As stated under *Sampling Considerations*, continuous in-process data sampling is excellent for understanding how a water system performs during all of its various usage and maintenance events in real time, but is too much data for QC purposes. Therefore, a justifiable fraction or averaging of the data can be used that is still representative of the overall water quality being used.

Packaged/sterile waters present a particular dilemma relative to the attributes of conductivity and TOC. The package

itself is the source of chemicals (inorganics and organics) that leach over time into the packaged water and can easily be detected by the conductivity and TOC tests. The irony of organic leaching from plastic packaging is that before the advent of bulk water TOC testing when the *Oxidizable Substances* test was the only “organic purity” test for both bulk and packaged/sterile water monographs in *USP*, that test’s insensitivity to many of the organic leachables from plastic and elastomeric packaging materials was largely unrealized, allowing organic levels in packaged/sterile water to be quite high (possibly many times the TOC specification for bulk water). Similarly, glass containers can also leach inorganics, such as sodium, which are easily detected by conductivity, but poorly detected by the former wet chemistry attribute tests. Most of these leachables are considered harmless by current perceptions and standards at the rather significant concentrations present. Nevertheless, they effectively degrade the quality of the high-purity waters placed into these packaging systems. Some packaging materials contain more leachables than others and may not be as suitable for holding water and maintaining its purity.

The attributes of conductivity and TOC tend to reveal more about the packaging leachables than they do about the water’s original purity. These currently “allowed” leachables could render the sterile packaged versions of originally equivalent bulk water essentially unsuitable for many uses where the bulk waters are perfectly adequate.

Therefore, to better control the ionic packaging leachables, *Water Conductivity* 〈645〉 is divided into two sections. The first is titled *Bulk Water*, which applies to *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and *Pure Steam*, and includes the three-stage conductivity testing instructions and specifications. The second is titled *Sterile Water*, which applies to *Sterile Purified Water*, *Sterile Water for Injection*, *Sterile Water for Inhalation*, and *Sterile Water for Irrigation*. The *Sterile Water* section includes conductivity specifications similar to the *Stage 2* testing approach because it is intended as a laboratory test, and these sterile waters were made from bulk water that already complied with the three-stage conductivity test. In essence, packaging leachables are the primary target “analytes” of the conductivity specifica-

Table 1. Contributing Ion Conductivities of the Chloride–Ammonia Model as a Function of pH
(in atmosphere-equilibrated water at 25°)

pH	Conductivity ($\mu S/cm$)						Combined Conductivities	Stage 3 Limit
	H^+	OH^-	HCO_3^-	Cl^-	Na^+	NH_4^+		
5.0	3.49	0	0.02	1.01	0.19	0	4.71	4.7
5.1	2.77	0	0.02	1.01	0.29	0	4.09	4.1
5.2	2.20	0	0.03	1.01	0.38	0	3.62	3.6
5.3	1.75	0	0.04	1.01	0.46	0	3.26	3.3
5.4	1.39	0	0.05	1.01	0.52	0	2.97	3.0
5.5	1.10	0	0.06	1.01	0.58	0	2.75	2.8
5.6	0.88	0	0.08	1.01	0.63	0	2.60	2.6
5.7	0.70	0	0.10	1.01	0.68	0	2.49	2.5
5.8	0.55	0	0.12	1.01	0.73	0	2.41	2.4
5.9	0.44	0	0.16	1.01	0.78	0	2.39	2.4
6.0	0.35	0	0.20	1.01	0.84	0	2.40	2.4
6.1	0.28	0	0.25	1.01	0.90	0	2.44	2.4
6.2	0.22	0	0.31	1.01	0.99	0	2.53	2.5
6.3	0.18	0	0.39	0.63	0	1.22	2.42	2.4
6.4	0.14	0.01	0.49	0.45	0	1.22	2.31	2.3
6.5	0.11	0.01	0.62	0.22	0	1.22	2.18	2.2
6.6	0.09	0.01	0.78	0	0.04	1.22	2.14	2.1
6.7	0.07	0.01	0.99	0	0.27	1.22	2.56	2.6
6.8	0.06	0.01	1.24	0	0.56	1.22	3.09	3.1
6.9	0.04	0.02	1.56	0	0.93	1.22	3.77	3.8
7.0	0.03	0.02	1.97	0	1.39	1.22	4.63	4.6

tions in the *Sterile Water* section of *Water Conductivity* (645). The effect on potential leachables from different container sizes is the rationale for having two different specifications, one for small packages containing nominal volumes of 10 mL or less and another for larger packages. These conductivity specifications are harmonized with the *European Pharmacopoeia* conductivity specifications for *Sterile Water for Injection*. All monographed waters, except *Bacteriostatic Water for Injection*, have a conductivity specification that directs the user to either the *Bulk Water* or the *Sterile Water* section of *Water Conductivity* (645). For the sterile packaged water monographs, this water conductivity specification replaces the redundant wet chemistry limit tests intended for inorganic contaminants that had previously been specified in these monographs.

Controlling the organic purity of these sterile packaged waters, particularly those in plastic packaging, is more challenging. Although the TOC test can better detect and therefore be better used to monitor and control these impurities than the current *Oxidizable Substances* test, the latter has many decades-old precedents and flexibility with the variety of packaging types and volumes applicable to these sterile packaged waters. Nevertheless, TOC testing of these currently allowed sterile, plastic-packaged waters reveals substantial levels of plastic-derived organic leachables that render the water perhaps orders of magnitude less organically pure than typically achieved with bulk waters. Therefore, usage of these packaged waters for analytical, manufacturing, and cleaning applications should only be exercised after suitability of the waters' purity for the application has been assured.

■ There is an analogous partitioning of *Total Organic Carbon* (643) to better control the organic packaging leachables. The first part is titled *Bulk Water*, which applies to the TOC method for *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and *Pure Steam*. The second part is titled *Sterile Water*, which applies to the TOC method for *Sterile Purified Water*, *Sterile Water for Injection*, *Sterile Water for Inhalation*, and *Sterile Water for Irrigation*. For these sterile waters, the TOC method is provided as an alternative test to the *Oxidizable Substances* test. The TOC limits for the sterile waters are set to higher values than the TOC limits for bulk waters. ■ (USP36)

MICROBIAL CONSIDERATIONS

The major exogenous source of microbial contamination of bulk pharmaceutical water is source or feed water. Feed water quality must, at a minimum, meet the quality attributes of Drinking Water for which the level of coliforms is regulated. A wide variety of other microorganisms, chiefly Gram-negative bacteria, may be present in the incoming water. These microorganisms may compromise subsequent purification steps. Examples of other potential exogenous sources of microbial contamination include unprotected vents, faulty air filters, ruptured rupture disks, backflow from contaminated outlets, unsanitized distribution system "openings" including routine component replacements, inspections, repairs, and expansions, inadequate drain and air-breaks, and replacement activated carbon, deionizer resins, and regenerant chemicals. In these situations, the exogenous contaminants may not be normal aquatic bacteria but rather microorganisms of soil or even of human origin. The detection of nonaquatic microorganisms may be an indication of a system component failure, which should trigger investigations that will remediate their source. Sufficient care should be given to system design and maintenance in order to minimize microbial contamination from these exogenous sources.

Unit operations can be a major source of endogenous microbial contamination. Microorganisms present in feed water may adsorb to carbon bed, deionizer resins, filter membranes, and other unit operation surfaces and initiate the formation of a biofilm. In a high-purity water system,

biofilm is an adaptive response by certain microorganisms to survive in this low nutrient environment. Downstream colonization can occur when microorganisms are shed from existing biofilm-colonized surfaces and carried to other areas of the water system. Microorganisms may also attach to suspended particles such as carbon bed fines or fractured resin particles. When the microorganisms become planktonic, they serve as a source of contamination to subsequent purification equipment (compromising its functionality) and to distribution systems.

Another source of endogenous microbial contamination is the distribution system itself. Microorganisms can colonize pipe surfaces, rough welds, badly aligned flanges, valves, and unidentified dead legs, where they proliferate, forming a biofilm. The smoothness and composition of the surface may affect the rate of initial microbial adsorption, but once adsorbed, biofilm development, unless otherwise inhibited by sanitizing conditions, will occur regardless of the surface. Once formed, the biofilm becomes a continuous source of microbial contamination.

ENDOTOXIN CONSIDERATIONS

Endotoxins are lipopolysaccharides found in and shed from the cell envelope that is external to the cell wall of Gram-negative bacteria. Gram-negative bacteria that form biofilms can become a source of endotoxins in pharmaceutical waters. Endotoxins may occur as clusters of lipopolysaccharide molecules associated with living microorganisms, fragments of dead microorganisms or the polysaccharide slime surrounding biofilm bacteria, or as free molecules. The free form of endotoxins may be released from cell surfaces of the bacteria that colonize the water system, or from the feed water that may enter the water system. Because of the multiplicity of endotoxin sources in a water system, endotoxin quantitation in a water system is not a good indicator of the level of biofilm abundance within a water system.

Endotoxin levels may be minimized by controlling the introduction of free endotoxins and microorganisms in the feed water and minimizing microbial proliferation in the system. This may be accomplished through the normal exclusion or removal action afforded by various unit operations within the treatment system as well as through system sanitization. Other control methods include the use of ultrafilters or charge-modified filters, either in-line or at the point of use. The presence of endotoxins may be monitored as described in the chapter *Bacterial Endotoxins Test* (85).

MICROBIAL ENUMERATION CONSIDERATIONS

The objective of a water system microbiological monitoring program is to provide sufficient information to control and assess the microbiological quality of the water produced. Product quality requirements should dictate water quality specifications. An appropriate level of control may be maintained by using data trending techniques and, if necessary, limiting specific contraindicated microorganisms. Consequently, it may not be necessary to detect all of the microorganisms species present in a given sample. The monitoring program and methodology should indicate adverse trends and detect microorganisms that are potentially harmful to the finished product, process, or consumer. Final selection of method variables should be based on the individual requirements of the system being monitored.

It should be recognized that there is no single method that is capable of detecting all of the potential microbial contaminants of a water system. The methods used for microbial monitoring should be capable of isolating the numbers and types of organisms that have been deemed significant relative to in-process system control and product impact for each individual system. Several criteria should be considered when selecting a method to monitor the micro-

bial content of a pharmaceutical water system. These include method sensitivity, range of organisms types or species recovered, sample processing throughput, incubation period, cost, and methodological complexity. An alternative consideration to the use of the classical “culture” approaches is a sophisticated instrumental or rapid test method that may yield more timely results. However, care must be exercised in selecting such an alternative approach to ensure that it has both sensitivity and correlation to classical culture approaches, which are generally considered the accepted standards for microbial enumeration.

Consideration should also be given to the timeliness of microbial enumeration testing after sample collection. The number of detectable planktonic bacteria in a sample collected in a scrupulously clean sample container will usually drop as time passes. The planktonic bacteria within the sample will tend to either die or to irretrievably adsorb to the container walls, reducing the number of viable planktonic bacteria that can be withdrawn from the sample for testing. The opposite effect can also occur if the sample container is not scrupulously clean and contains a low concentration of some microbial nutrient that could promote microbial growth within the sample container. Because the number of recoverable bacteria in a sample can change positively or negatively over time after sample collection, it is best to test the samples as soon as possible after being collected. If it is not possible to test the sample within about 2 h of collection, the sample should be held at refrigerated temperatures (2°–8°) for a maximum of about 12 h to maintain the microbial attributes until analysis. In situations where even this is not possible (such as when using off-site contract laboratories), testing of these refrigerated samples should be performed within 48 h after sample collection. In the delayed testing scenario, the recovered microbial levels may not be the same as would have been recovered had the testing been performed shortly after sample collection. Therefore, studies should be performed to determine the existence and acceptability of potential microbial enumeration aberrations caused by protracted testing delays.

The Classical Culture Approach

Classical culture approaches for microbial testing of water include but are not limited to pour plates, spread plates, membrane filtration, and most probable number (MPN) tests. These methods are generally easy to perform, are less expensive, and provide excellent sample processing throughput. Method sensitivity can be increased via the use of larger sample sizes. This strategy is used in the membrane filtration method. Culture approaches are further defined by the type of medium used in combination with the incubation temperature and duration. This combination should be selected according to the monitoring needs presented by a specific water system as well as its ability to recover the microorganisms of interest: those that could have a detrimental effect on the product or process uses as well as those that reflect the microbial control status of the system.

There are two basic forms of media available for traditional microbiological analysis: “high nutrient” and “low nutrient”. High-nutrient media, such as plate count agar (TGYA) and m-HPC agar (formerly m-SPC agar), are intended as general media for the isolation and enumeration of heterotrophic or “copiotrophic” bacteria. Low-nutrient media, such as R2A agar and NWRI agar (HPCA), may be beneficial for isolating slow-growing “oligotrophic” bacteria and bacteria that require lower levels of nutrients to grow optimally. Often some facultative oligotrophic bacteria are able to grow on high-nutrient media and some facultative copiotrophic bacteria are able to grow on low-nutrient media, but this overlap is not complete. Low-nutrient and high-nutrient cultural approaches may be concurrently used,

especially during the validation of a water system, as well as periodically thereafter. This concurrent testing could determine if any additional numbers or types of bacteria can be preferentially recovered by one of the approaches. If so, the impact of these additional isolates on system control and the end uses of the water could be assessed. Also, the efficacy of system controls and sanitization on these additional isolates could be assessed.

Duration and temperature of incubation are also critical aspects of a microbiological test method. Classical methodologies using high-nutrient media are typically incubated at 30°–35° for 48–72 h. Because of the flora in certain water systems, incubation at lower temperatures (e.g., 20°–25°) for longer periods (e.g., 5–7 days) can recover higher microbial counts when compared to classical methods. Low-nutrient media are designed for these lower temperature and longer incubation conditions (sometimes as long as 14 days to maximize recovery of very slow-growing oligotrophs or sanitant-injured microorganisms), but even high-nutrient media can sometimes increase their recovery with these longer and cooler incubation conditions. Whether or not a particular system needs to be monitored using high- or low-nutrient media with higher or lower incubation temperatures or shorter or longer incubation times should be determined during or prior to system validation and periodically reassessed as the microbial flora of a new water system gradually establish a steady state relative to its routine maintenance and sanitization procedures. The establishment of a “steady state” can take months or even years and can be perturbed by a change in use patterns, a change in routine and preventative maintenance or sanitization procedures, and frequencies, or any type of system intrusion, such as for component replacement, removal, or addition. The decision to use longer incubation periods should be made after balancing the need for timely information and the type of corrective actions required when an alert or action level is exceeded with the ability to recover the microorganisms of interest.

The advantages gained by incubating for longer times, namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and to take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes. In no case, however, should incubation at 30°–35° be less than 48 h or less than 96 h at 20°–25°.

Normally, the microorganisms that can thrive in extreme environments are best cultivated in the laboratory using conditions simulating the extreme environments from which they were taken. Therefore, thermophilic bacteria might be able to exist in the extreme environment of hot pharmaceutical water systems, and if so, could only be recovered and cultivated in the laboratory if similar thermal conditions were provided. Thermophilic aquatic microorganisms do exist in nature, but they typically derive their energy for growth from harnessing the energy from sunlight, from oxidation/reduction reactions of elements such as sulfur or iron, or indirectly from other microorganisms that do derive their energy from these processes. Such chemical/nutritional conditions do not exist in high-purity water systems, whether ambient or hot. Therefore, it is generally considered pointless to search for thermophiles from hot pharmaceutical water systems owing to their inability to grow there.

The microorganisms that inhabit hot systems tend to be found in much cooler locations within these systems, for example, within use-point heat exchangers or transfer hoses. If this occurs, the kinds of microorganisms recovered are usually of the same types that might be expected from ambient water systems. Therefore, the mesophilic microbial cultivation conditions described later in this chapter are usually adequate for their recovery.

“Instrumental” Approaches

Examples of instrumental approaches include microscopic visual counting techniques (e.g., epifluorescence and immunofluorescence) and similar automated laser scanning approaches and radiometric, impedometric, and biochemically based methodologies. These methods all possess a variety of advantages and disadvantages. Advantages could be their precision and accuracy or their speed of test result availability as compared to the classical cultural approach. In general, instrument approaches often have a shorter lead time for obtaining results, which could facilitate timely system control. This advantage, however, is often counterbalanced by limited sample processing throughput due to extended sample collection time, costly and/or labor-intensive sample processing, or other instrument and sensitivity limitations.

Furthermore, instrumental approaches are typically destructive, precluding subsequent isolate manipulation for characterization purposes. Generally, some form of microbial isolate characterization, if not full identification, may be a required element of water system monitoring. Consequently, culturing approaches have traditionally been preferred over instrumental approaches because they offer a balance of desirable test attributes and post-test capabilities.

Suggested Methodologies

The following general methods were originally derived from *Standard Methods for the Examination of Water and Wastewater*, 17th Edition, American Public Health Association, Washington, DC 20005. Although this publication has undergone several revisions since its first citation in this chapter, the methods are still considered appropriate for establishing trends in the number of colony-forming units observed in the routine microbiological monitoring of pharmaceutical waters. It is recognized, however, that other combinations of media and incubation time and temperature may occasionally or even consistently result in higher numbers of colony-forming units being observed and/or different species being recovered.

The extended incubation periods that are usually required by some of the alternative methods available offer disadvantages that may outweigh the advantages of the higher counts that may be obtained. The somewhat higher baseline counts that might be observed using alternate cultural conditions would not necessarily have greater utility in detecting an excursion or a trend. In addition, some alternate cultural conditions using low-nutrient media tend to lead to the development of microbial colonies that are much less differentiated in colonial appearance, an attribute that microbiologists rely on when selecting representative microbial types for further characterization. It is also ironical that the nature of some of the slow growers and the extended incubation times needed for their development into visible colonies may also lead to those colonies being largely nonviable, which limits their further characterization and precludes their subculture and identification.

Methodologies that can be suggested as generally satisfactory for monitoring pharmaceutical water systems are as follows. However, it must be noted that these are not referee methods nor are they necessarily optimal for recovering microorganisms from all water systems. The users should determine through experimentation with various approaches which methodologies are best for monitoring their water systems for in-process control and quality control purposes as well as for recovering any contraindicated species they may have specified.

<i>Drinking Water</i>	Pour Plate Method or Membrane Filtration Method ^a
	Sample volume—1.0 mL minimum ^b Growth medium—Plate Count Agar ^c Incubation time—48–72 h minimum Incubation temperature—30°–35°
<i>Purified Water</i>	Pour Plate Method or Membrane Filtration Method ^a
	Sample volume—1.0 mL minimum ^b Growth medium—Plate Count Agar ^c Incubation time—48–72 h minimum Incubation temperature—30°–35°
<i>Water for Injection</i>	Membrane Filtration Method ^a
	Sample volume—100 mL minimum ^b Growth medium—Plate Count Agar ^c Incubation time—48–72 h minimum Incubation temperature—30°–35°

^aA membrane filter with a rating of 0.45 µm is generally considered preferable, although the cellular width of some of the bacteria in the sample may be narrower than this. The efficiency of the filtration process still allows the retention of a very high percentage of these smaller cells and is adequate for this application. Filters with smaller ratings may be used if desired, but for a variety of reasons the ability of the retained cells to develop into visible colonies may be compromised, so count accuracy must be verified by a reference approach.

^bWhen colony counts are low to undetectable using the indicated minimum sample volume, it is generally recognized that a larger sample volume should be tested in order to gain better assurance that the resulting colony count is more statistically representative. The sample volume to consider testing is dependent on the user's need to know (which is related to the established alert and action levels and the water system's microbial control capabilities) and the statistical reliability of the resulting colony count. In order to test a larger sample volume, it may be necessary to change testing techniques, e.g., changing from a pour plate to a membrane filtration approach. Nevertheless, in a very low to nil count scenario, a maximum sample volume of around 250–300 mL is usually considered a reasonable balance of sample collecting and processing ease and increased statistical reliability. However, when sample volumes larger than about 2 mL are needed, they can only be processed using the membrane filtration method.

^cAlso known as Standard Methods Agar, Standard Methods Plate Count Agar, or TGYA, this medium contains tryptone (pancreatic digest of casein), glucose, and yeast extract.

IDENTIFICATION OF MICROORGANISMS

Identifying the isolates recovered from water monitoring methods may be important in instances where specific waterborne microorganisms may be detrimental to the products or processes in which the water is used. Microorganism information such as this may also be useful when identifying the source of microbial contamination in a product or process. Often a limited group of microorganisms is routinely recovered from a water system. After repeated recovery and characterization, an experienced microbiologist may become proficient at their identification based on only a few recognizable traits such as colonial morphology and staining characteristics. This may allow for a reduction in the number of identifications to representative colony types, or, with proper analyst qualification, may even allow testing shortcuts to be taken for these microbial identifications.

ALERT AND ACTION LEVELS AND SPECIFICATIONS

Although the use of alert and action levels is most often associated with microbial data, they can be associated with any attribute. In pharmaceutical water systems, almost every

quality attribute, other than microbial quality, can be very rapidly determined with near-real time results. These short-delay data can give immediate system performance feedback, serving as ongoing process control indicators. However, because some attributes may not continuously be monitored or have a long delay in data availability (like microbial monitoring data), properly established *Alert and Action Levels and Specifications* can serve as an early warning or indication of a potentially approaching quality shift occurring between or at the next periodic monitoring. In a validated water system, process controls should yield relatively constant and more than adequate values for these monitored attributes such that their *Alert and Action Levels and Specifications* are infrequently breached.

As process control indicators, alert and action levels are designed to allow remedial action to occur that will prevent a system from deviating completely out of control and producing water unfit for its intended use. This “intended use” minimum quality is sometimes referred to as a “specification” or “limit”. In the opening paragraphs of this chapter, rationale was presented for no microbial specifications being included within the body of the bulk water (*Purified Water* and *Water for Injection*) monographs. This does not mean that the user should not have microbial specifications for these waters. To the contrary, in most situations such specifications should be established by the user. The microbial specification should reflect the maximum microbial level at which the water is still fit for use without compromising the quality needs of the process or product where the water is used. Because water from a given system may have many uses, the most stringent of these uses should be used to establish this specification.

Where appropriate, a microbial specification could be qualitative as well as quantitative. In other words, the number of total microorganisms may be as important as the number of a specific microorganism or even the absence of a specific microorganism. Microorganisms that are known to be problematic could include opportunistic or overt pathogens, nonpathogenic indicators of potentially undetected pathogens, or microorganisms known to compromise a process or product, such as by being resistant to a preservative or able to proliferate in or degrade a product. These microorganisms comprise an often ill-defined group referred to as “objectionable microorganisms”. Because objectionable is a term relative to the water’s use, the list of microorganisms in such a group should be tailored to those species with the potential to be present and problematic. Their negative impact is most often demonstrated when they are present in high numbers, but depending on the species, an allowable level may exist, below which they may not be considered objectionable.

As stated above, alert and action levels for a given process control attribute are used to help maintain system control and avoid exceeding the pass/fail specification for that attribute. Alert and action levels may be both quantitative and qualitative. They may involve levels of total microbial counts or recoveries of specific microorganisms. Alert levels are events or levels that, when they occur or are exceeded, indicate that a process may have drifted from its normal operating condition. Alert level excursions constitute a warning and do not necessarily require a corrective action. However, alert level excursions usually lead to the alerting of personnel involved in water system operation as well as QA. Alert level excursions may also lead to additional monitoring with more intense scrutiny of resulting and neighboring data as well as other process indicators. Action levels are events or higher levels that, when they occur or are exceeded, indicate that a process is probably drifting from its normal operating range. Examples of kinds of action level “events” include exceeding alert levels repeatedly; or in multiple simultaneous locations, a single occurrence of exceeding a higher microbial level; or the individual or repeated recovery of specific objectionable microorganisms. Exceeding an action level should lead to immediate notification of both QA and personnel involved in water system operations so that

corrective actions can immediately be taken to bring the process back into its normal operating range. Such remedial actions should also include efforts to understand and eliminate or at least reduce the incidence of a future occurrence. A root cause investigation may be necessary to devise an effective preventative action strategy. Depending on the nature of the action level excursion, it may also be necessary to evaluate its impact on the water uses during that time. Impact evaluations may include delineation of affected batches and additional or more extensive product testing. It may also involve experimental product challenges.

Alert and action levels should be derived from an evaluation of historic monitoring data called a trend analysis. Other guidelines on approaches that may be used, ranging from “inspectional” to statistical evaluation of the historical data have been published. The ultimate goal is to understand the normal variability of the data during what is considered a typical operational period. Then, trigger points or levels can be established that will signal when future data may be approaching (alert level) or exceeding (action level) the boundaries of that “normal variability”. Such alert and action levels are based on the control capability of the system as it was being maintained and controlled during that historic period of typical control.

In new water systems where there is very limited or no historic data from which to derive data trends, it is common to simply establish initial alert and action levels based on a combination of equipment design capabilities but below the process and product specifications where water is used. It is also common, especially for ambient water systems, to microbiologically “mature” over the first year of use. By the end of this period, a relatively steady state microbial population (microorganism types and levels) will have been allowed or promoted to develop as a result of the collective effects of routine system maintenance and operation, including the frequency of unit operation rebeddings, backwashings, regenerations, and sanitizations. This microbial population will typically be higher than was seen when the water system was new, so it should be expected that the data trends (and the resulting alert and action levels) will increase over this “maturation” period and eventually level off.

A water system should be designed so that performance-based alert and action levels are well below water specifications. With poorly designed or maintained water systems, the system owner may find that initial new system microbial levels were acceptable for the water uses and specifications, but the mature levels are not. This is a serious situation, which if not correctable with more frequent system maintenance and sanitization, may require expensive water system renovation or even replacement. Therefore, it cannot be overemphasized that water systems should be designed for ease of microbial control, so that when monitored against alert and action levels, and maintained accordingly, the water continuously meets all applicable specifications.

An action level should not be established at a level equivalent to the specification. This leaves no room for remedial system maintenance that could avoid a specification excursion. Exceeding a specification is a far more serious event than an action level excursion. A specification excursion may trigger an extensive finished product impact investigation, substantial remedial actions within the water system that may include a complete shutdown, and possibly even product rejection.

Another scenario to be avoided is the establishment of an arbitrarily high and usually nonperformance-based action level. Such unrealistic action levels deprive users of meaningful indicator values that could trigger remedial system maintenance. Unrealistically high action levels allow systems to grow well out of control before action is taken, when their intent should be to catch a system imbalance before it goes wildly out of control.

Because alert and action levels should be based on actual system performance, and the system performance data are generated by a given test method, it follows that those alert and action levels should be valid only for test results gener-

ated by the same test method. It is invalid to apply alert and action level criteria to test results generated by a different test method. The two test methods may not equivalently recover microorganisms from the same water samples. Similarly invalid is the use of trend data to derive alert and action levels for one water system, but applying those alert and action levels to a different water system. Alert and action levels are water system and test method specific.

Nevertheless, there are certain maximum microbial levels above which action levels should never be established. Water systems with these levels should unarguably be considered out of control. Using the microbial enumeration methodologies suggested above, generally considered maximum action levels are 100 cfu/mL for *Purified Water* and 10 cfu/100 mL for *Water for Injection*. However, if a given water system controls microorganisms much more tightly than these levels, appropriate alert and action levels should be established from these tighter control levels so that they can truly indicate when water systems may be starting to trend out of control. These in-process microbial control parameters should be established well below the user-defined microbial specifications that delineate the water's fitness for use.

Special consideration is needed for establishing maximum microbial action levels for *Drinking Water* because the water is often delivered to the facility in a condition over which the user has little control. High microbial levels in *Drinking Water* may be indicative of a municipal water system upset, broken water main, or inadequate disinfection, and therefore, potential contamination with objectionable microorganisms. Using the suggested microbial enumeration methodology, a reasonable maximum action level for *Drinking Water* is 500 cfu/mL. Considering the potential concern for objectionable microorganisms raised by such high microbial levels in the feed water, informing the municipality of the problem so they may begin corrective actions should be an immediate first step. In-house remedial actions may or may not also be needed, but could include performing additional coliform testing on the incoming water and pretreating the water with either additional chlorination or UV light irradiation or filtration, or a combination of approaches.

Add the following:

•<1724> SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in

performance testing of semisolid drug products. General chapter *Topical and Transdermal Drug Products—Product Quality Tests* <3> provides information related to product quality tests for topical and transdermal dosage forms, *Drug Release* <724> provides procedures and details for testing drug release from transdermal systems, and this chapter <1724> provides procedures for determining drug release from semisolid dosage forms.

INTRODUCTION

This chapter provides general information for in vitro testing of semisolid drug products. Semisolid dosage forms include creams, ointments, gels, and lotions. Semisolid dosage forms may be considered extended-release preparations, and their drug release depends largely on the formulation and manufacturing process. The release rate of a given product from different manufacturers is likely to be different.

DRUG PRODUCT QUALITY AND PERFORMANCE TESTS

A USP drug product monograph contains tests, analytical procedures, and acceptance criteria. Drug product tests are divided into two categories: (1) those that assess general quality attributes, and (2) those that assess product performance, e.g., in vitro release of the drug substance from the drug product. Quality tests assess the integrity of the dosage form, but performance tests, such as drug release, assess attributes that relate to in vivo drug performance. Taken together, quality and performance tests are intended to ensure the identity, strength, quality, purity, comparability, and performance of semisolid drug products.

Details of drug product quality tests for semisolid drug products can be found in chapter <3>. Product performance tests for semisolid drug products are conducted to assess drug release from manufactured pharmaceutical dosage forms. In vitro performance tests for semisolid products do not, however, directly predict the in vivo performance of drugs, as the primary factor that impacts bioavailability and clinical performance are the barrier properties of the epithelia to which the product is applied (epidermal or mucosal tissues). Although product performance tests do not directly measure bioavailability and relative bioavailability (bioequivalence), they can detect in vitro changes that may correspond to altered in vivo performance of the dosage form. These changes may arise from changes in physicochemical characteristics of the drug substance and/or excipients or to the formulation itself, changes in the manufacturing process, shipping and storage effects, aging effects, and other formulation and/or process factors.

At present, a product performance test is available to evaluate in vitro drug release for creams, ointments, lotions, and gels. Several available apparatus can be used for this evaluation, including the vertical diffusion cell, immersion cell, and a special cell used with USP Apparatus 4. Because of the significant impact of in vitro test parameters, such as release media, porous membrane and dosing, and the interaction of these parameters with a given drug product, the primary use of in vitro drug release testing is comparison testing in which any difference in delivery rate is undesirable. Drug release testing is most suitable for evaluation of small formulation and process changes, manufacturing site changes, and stability testing. The evaluation or comparison of large formulation changes may provide unmeaningful results, unless extensive validation is performed to select test parameters that ensure that the sensitivity of the test is meaningfully correlated with in vivo performance. The only required regulatory use of the in vitro release test is to determine the acceptability of minor process and/or formulation changes in approved semisolid dosage forms (see *FDA Guidance for Industry—Nonsterile Semisolid Dosage Forms—Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Con-*

trols; In Vitro Release Testing and In Vivo Bioequivalence Documentation; available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070930.pdf>).

This chapter provides general information for testing in vitro performance of semisolid drug products.

IN VITRO PERFORMANCE TESTS

Theory

The diffusion cell is a reliable and reproducible means of measuring drug release from semisolid dosage forms. A thick layer of the semisolid product under evaluation is placed in contact with a medium in a reservoir, and the latter acts as a receptor when the drug substance diffuses through the formulation, across the membrane, and into the reservoir. Diffusion occurs across an inert, highly permeable support membrane. The membrane is intended to keep the product and the receptor medium separate and distinct. Membranes should offer the least possible diffusional resistance and should not be rate controlling. Samples are withdrawn from the receptor chamber, typically at 1-h intervals over a 4–6 h period.

After a short lag period, release of drug from the semisolid dosage form is kinetically described by diffusion of a chemical out of a semi-infinite medium into a sink. The momentary release rate tracks the depth of penetration of the forming gradient within the semisolid. Beginning at the moment when the receding boundary layer's diffusional resistance assumes dominance of the kinetics of release, the amount of the drug released, m , becomes proportional to \sqrt{t} (where t = time) for solution, suspension, or emulsion semisolid system alike. The momentary rate of drug release, dm/dt , becomes proportional to $1/\sqrt{t}$, which reflects the slowing of drug release with the passage of time. The reservoir is kept large so that over the entire course of the experiment, the concentration of the drug released into a medium remains highly dilute relative to the concentration of drug dissolved in the semisolid. In these circumstances, drug release is said to take place into a diffusional sink.

When a drug is totally in solution in the dosage form, the amount of drug released as a function of time can be described by Equation 1:

$$m = 2 \times C_0 \sqrt{\frac{Dt}{\pi}}$$

where m is the amount of drug released into the sink per cm^2 , C_0 is the drug concentration in the releasing matrix, and D is the drug diffusion coefficient through the matrix.

A plot of m versus \sqrt{t} will be linear with a slope of:

$$2 \times C_0 \sqrt{\frac{D}{\pi}}$$

Equation 2 describes drug release when the drug is in the form of a suspension in the dosage form:

$$m = \sqrt{2 \times D_m \times C_s \left(Q - \frac{C_s}{2} \right) \times t}$$

where D_m is the drug diffusion coefficient in the semisolid matrix, C_s is the drug solubility in the releasing matrix, and Q is the total amount of the drug in solution and suspended in the matrix. When $Q \gg C_s$, Equation 2 simplifies to Equation 3:

$$m = \sqrt{2 \times Q \times D_m \times C_s \times t}$$

A plot of m versus \sqrt{t} will be linear with a slope of:

$$m = \sqrt{2 \times Q \times D_m \times C_s}$$

Coarse particles may dissolve so slowly that the moving boundary layer recedes to some extent behind the particles. That situation introduces noticeable curvature in the \sqrt{t} plot because of a particle size effect.

During release rate experiments, reasonable attempts should be made to keep the composition of the formulation intact over the releasing period.

Drug Release Rate Determination Using Vertical Diffusion Cell Apparatus

Many vertical diffusion cell (VDC) systems are composed of 6-cell units. Each VDC cell assembly consists of two chambers (a donor chamber and a receptor chamber) separated by a membrane and held together by a clamp, screw top, or other means (see *Figure 1–Model A*, *Figure 2–Model B*, and *Figure 3–Model C*). Other diffusion cells that are similar in general design also can be used. In the donor chamber, the semisolid dosage form sample sits on a synthetic, inert, highly permeable support membrane. For the VDC Model A, the sample sits on the support membrane within the cavity of the sample chamber covered with a glass disk.

Typically, amounts of the semisolid sample NLT 200 mg are used. Diffusive communication between the semisolid sample and the reservoir takes place through the support membrane. The membrane is intended to keep the drug product sample and receptor medium separate and distinct. A heating jacket or a suitable device should be used to maintain the temperature within the cell. The release rate experiment is carried out at $32 \pm 1^\circ$, except in the case of vaginal drug products for which the temperature should be $37 \pm 1^\circ$. Usually a set of 6 cell assemblies are operated together at one time (i.e., single run). Sampling generally is performed over a 4–6 h time period, and the volume withdrawn is replaced with stock receptor medium. To achieve sink condition, the receptor medium must have a high capacity to dissolve the drug, and the drug concentration in the receptor medium at the end of the test ideally should be as low as possible. For each cell, the amount of drug released ($\mu\text{g}/\text{cm}^2$) at each sampling time (t_1 , t_2 , etc.) is determined, and the cumulative amount released plotted versus \sqrt{t} . The slope of the resulting line is a measure of the rate of drug release. The test is often conducted with a group of 6 or 12 cells per test run. The average of 6 slopes for each test and reference product is a measure of the drug release rate from the dosage form.

The VDC body (i.e., donor and receptor chambers) usually is made from borosilicate glass, although different materials may be used to manufacture the body and other parts of the VDC assembly. It is recommended that the cell assembly materials should not significantly react with, adsorb to, or absorb the test product or samples. The semisolid dosage form is placed on a membrane within the cavity of the dosage chamber that can be occluded. The diameters of the orifices of the donor chamber and receptor chamber, which define the dosage delivery surface area for the test, should be sized within $\pm 5\%$ of the specified diameter. The diameter of the donor and receptor chamber orifices may vary depending on the application. The receptor chamber orifice should never be smaller than the orifice of the donor chamber but should be fabricated to the same size as the donor chamber orifice. The design of the VDC should facilitate proper alignment of the donor chamber and the receptor orifice. The receptor chamber should be manufactured consistently with uniform height and geometry. All the cells should have the same nominal value, and the true volume should be measured for each individual cell.

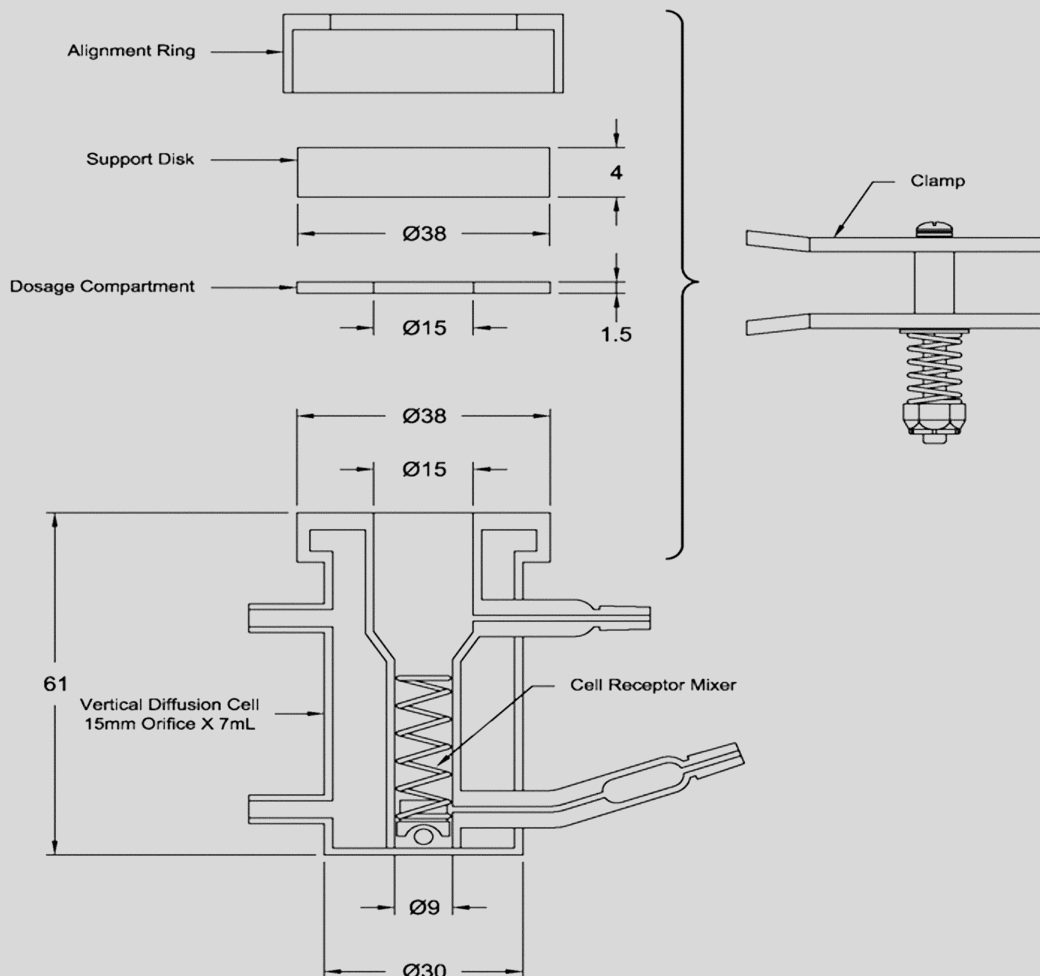


Figure 1. Vertical diffusion cell—Model A (All dimensions are in mm. All diameters are ± 0.5 mm. All lengths are ± 2 mm).

Care should be taken to minimize the intercell volume variability.

For the test, the VDC units are typically positioned in a stirrer rack (not depicted) that holds multiple VDC units (e.g., in sets of 6) in the correct orientation, providing magnetic stirring at a calibrated rate and facilitating the supply of circulating heated water flow to the water jacket of the VDC. The VDC rack is typically connected to a thermostatically controlled water bath recirculator.

The water from the circulating pump flows into the VDC heating jacket from the lower port and flows out from the upper port to facilitate the removal of any air bubbles formed in the heating jacket. A magnetic nonstick (Teflon-coated) stirring bar in the receptor chamber is used as the internal stirring mechanism. Aliquots of the receptor medium are drawn via the sampling arm at intervals throughout the test, and an equivalent volume of stock receptor medium replaced to the level of the calibration mark on the sampling arm.

MODEL A

The thickness of the sample chamber normally is 1.5 mm. This thickness should be sized within $\pm 10\%$ of the specified thickness. The glass support disk is used to occlude the semisolid dosage form. A receptor cell mixer and stirrer magnet are used as the internal stirring mechanism.

MODELS B AND C

Classic styles of VDC are depicted in *Figure 2* and *Figure 3* and illustrate minor design variations among qualified models.

Test Procedures: General

Before initiating testing, analysts should determine the volume of each VDC with the internal stirring device in place. During the entire test, the temperature of the receptor medium should be maintained at $32 \pm 1^\circ$, or $37 \pm 1^\circ$ for vaginal preparations. The rotational stirring rate tolerance should be $\pm 10\%$ of the rate in the method (normally 600

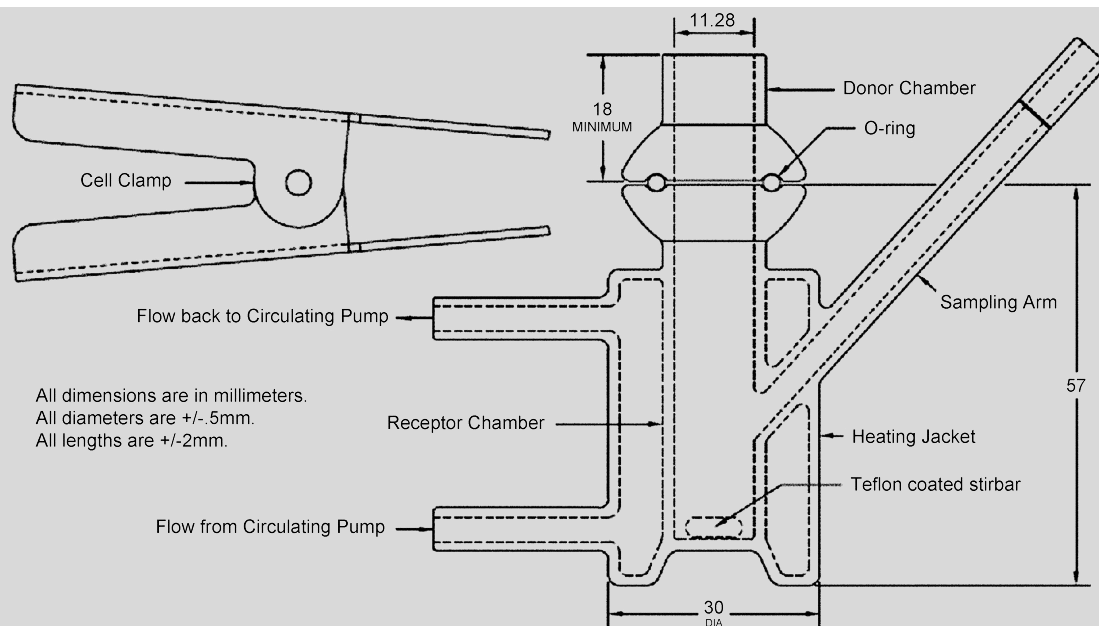


Figure 2. Vertical diffusion cell—Model B (All dimensions are in mm. All diameters are ± 0.5 mm. All lengths are ± 2 mm).

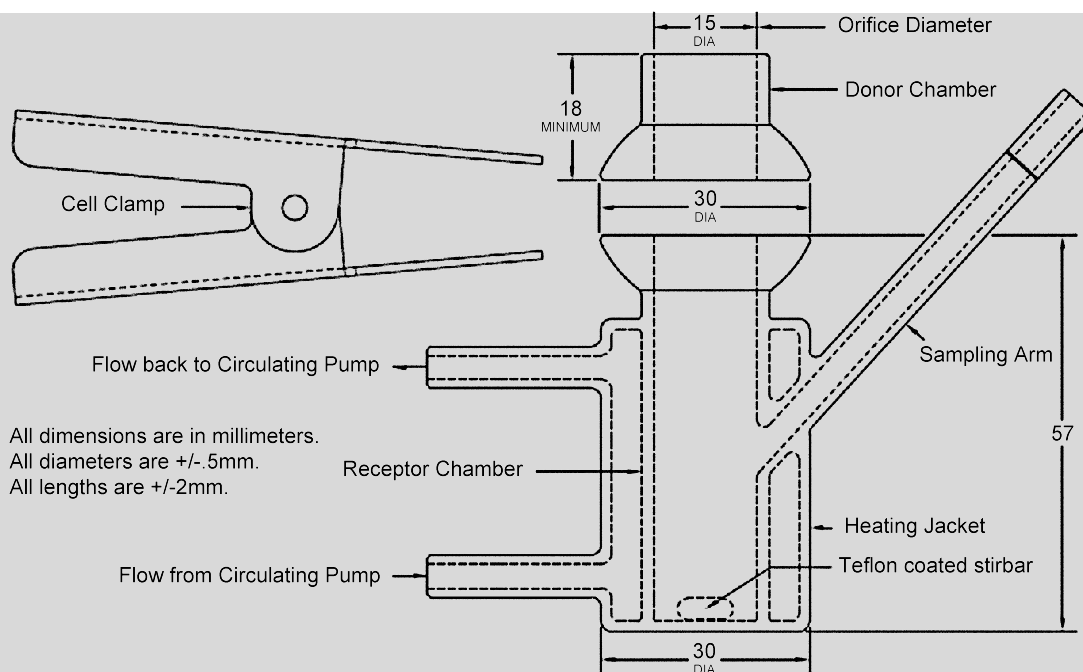


Figure 3. Vertical diffusion cell—Model C (All dimensions are in mm. All diameters are ± 0.5 mm. All lengths are ± 2 mm).

rpm). The rate of stirring should ensure adequate mixing of the receptor medium during the test period. Samples from each cell should be obtained at the specified times in the method within a tolerance of ± 2 min. Unless the method specifies otherwise, the qualification of the apparatus has been verified when analysts determine that the test temperature and stirring rate are within their specified requirements and a satisfactory performance verification test (i.e., drug release rate) results. Unless otherwise specified in the method, degas the medium using an appropriate technique. Determine the amount of drug in the receptor medium sample aliquots using a validated analytical procedure.

The following sections provide instructions for proper use of Models A, B, and C.

TEST PROCEDURES: MODEL A

With the stirring mechanism in place, fill the receptor chamber with the specified medium with the stirrers rotating and a positive meniscus covering the top of each cell. Allow time for the medium to equilibrate to the specified temperature. Stop the stirrer before placing the test sample on the cell. If necessary, saturate the membrane in the specified medium (generally the receptor medium) for 30 min.

Place the membrane on the donor chamber, and invert. Apply the material to be tested into the cavity of the sample chamber, spreading the semisolid out to fill the entire cavity of the sample chamber. Place the filled sample chamber on the receptor chamber with the membrane down and in contact with the receptor medium. During this procedure it is important to ensure that there are no bubbles beneath the membrane. Then assemble the complete cell. When the assembly of all donor and receptor chambers and remaining cell components (i.e., disk, alignment ring, and clamp) have been completed, turn on the stirring device, which constitutes the start of the test or time zero. Sampling is generally performed over a 4–6 h time period. Follow the specified sampling procedure, and collect an aliquot from each cell receptor chamber for analysis. With the stirrer stopped and using a syringe, replace the withdrawn volume with stock receptor medium warmed to the specific temperature, and resume stirring. During the sampling and medium replenishment process(es), ensure that bubbles are not introduced into the cell.

TEST PROCEDURES: MODELS B AND C

A nonstick (Teflon-coated) stir bar is placed within the receptor chamber of the VDC. The membrane specified in the test method is clamped atop the O-ring, if present, between the aligned donor and receptor chambers of the VDC. The exposed periphery of the joint between the donor and receptor compartments is sealed (e.g., circumscribed by stretched paraffin wax film).

The receptor chamber is filled with receptor medium via the sampling arm, unless it is already filled before the membrane is mounted. The VDC assembly is tilted in multiple orientations and inspected to ensure that any air bubbles trapped beneath the membrane, or within the receptor chamber, can escape via the sampling arm port. The volume of receptor medium is adjusted to the calibrated level marked on the sampling arm port. The membrane is allowed to equilibrate with the receptor medium, *in situ*, for at least 30 min prior to the application of the dosage form, or may be pre-incubated with a wetting solution (typically the receptor medium), as specified in the test method.

The VDC units are positioned in a stirrer rack. It is recommended that about 10–20 cm of slack should be available in the tubing connecting the ports of the VDC water jacket to the VDC rack to facilitate subsequent manipulation of the VDC during the test. The temperature set point of the water bath is adjusted before dosing so that the membrane is at the correct temperature. This can be verified by measuring the membrane temperature before dosing, using a calibrated infrared thermometer.

The stirring is initiated and can be maintained continuously throughout the test. The dosage form is evenly dispensed directly onto the membrane surface. The amount of sample recommended is NLT approximately 1.0 mL/cm² or 1.0 g/cm² to ensure a pseudo-infinite dose condition. Spreading of the sample typically starts at the outer edge and proceeds in an inward spiral pattern to assure full coverage of the edges of the dose area without air gaps. The placement of the sample constitutes the start of the test or time zero. The donor chamber is subsequently sealed with an occlusive film to prevent loss of any volatile components of the test formulation. The underside of the membrane is checked for air bubbles and, if any are seen, they are eliminated by tilting the apparatus in a manner that allows the air bubbles to escape. The receptor volume is confirmed at the calibrated volume mark and adjusted as necessary.

Before sample collections, typically every hour over the 4–6 h period following the introduction of the sample, the volume in the sampling arm is confirmed approximately 10

min before sampling and is adjusted to the calibration mark on the sampling arm as necessary. At predetermined intervals after starting the test, typically hourly for 6 h, analysts collect aliquots of the receptor medium (e.g., 150 µL) via the sampling arm, drawing from the well-mixed center of the receptor chamber. The VDC assembly is inspected for air bubbles, which are eliminated as necessary. Receptor medium is replaced to bring the receptor volume back to the level indicated on the sampling arm of the VDC.

Drug Release Rate Determination Using Immersion Cell Apparatus

The cell consists of the following components (see *Figure 4* and *Figure 5* for Model A, and *Figure 6* and *Figure 7* for Model B): a retaining or lock ring that secures the membrane to the cell body and ensures full contact with the sample; a washer that provides a leakproof seal between membrane, retaining ring, and cell body; the membrane (usually a synthetic membrane) that should retain the sample in the sample compartment; and the cell body that provides a variable depth reservoir for the sample. Model A also has an adjustment plate that allows operators to vary the volume of the reservoir within the cell body. The plate can be placed at the appropriate height for each test and can be completely removed to facilitate cleaning. An O-ring paired with the adjustment plate prevents leakage.

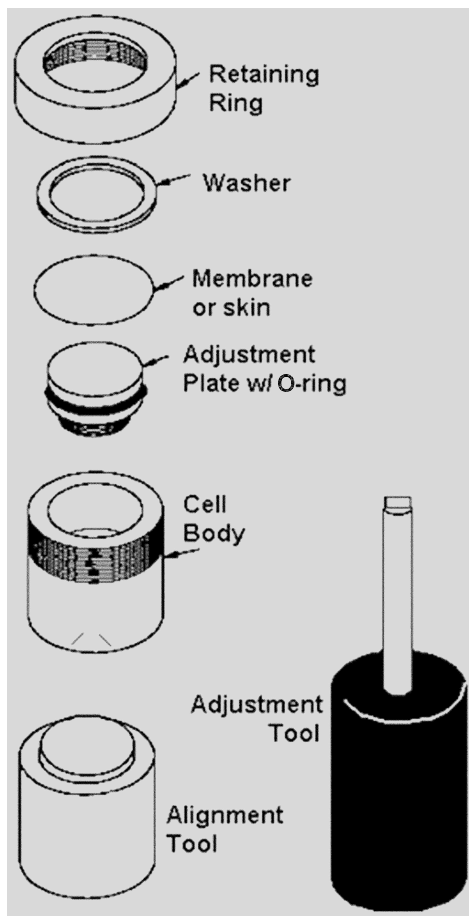


Figure 4. Immersion cell—Model A—Cell components.

ALL UNITS ARE MILLIMETERS (mm), UNLESS OTHERWISE NOTED

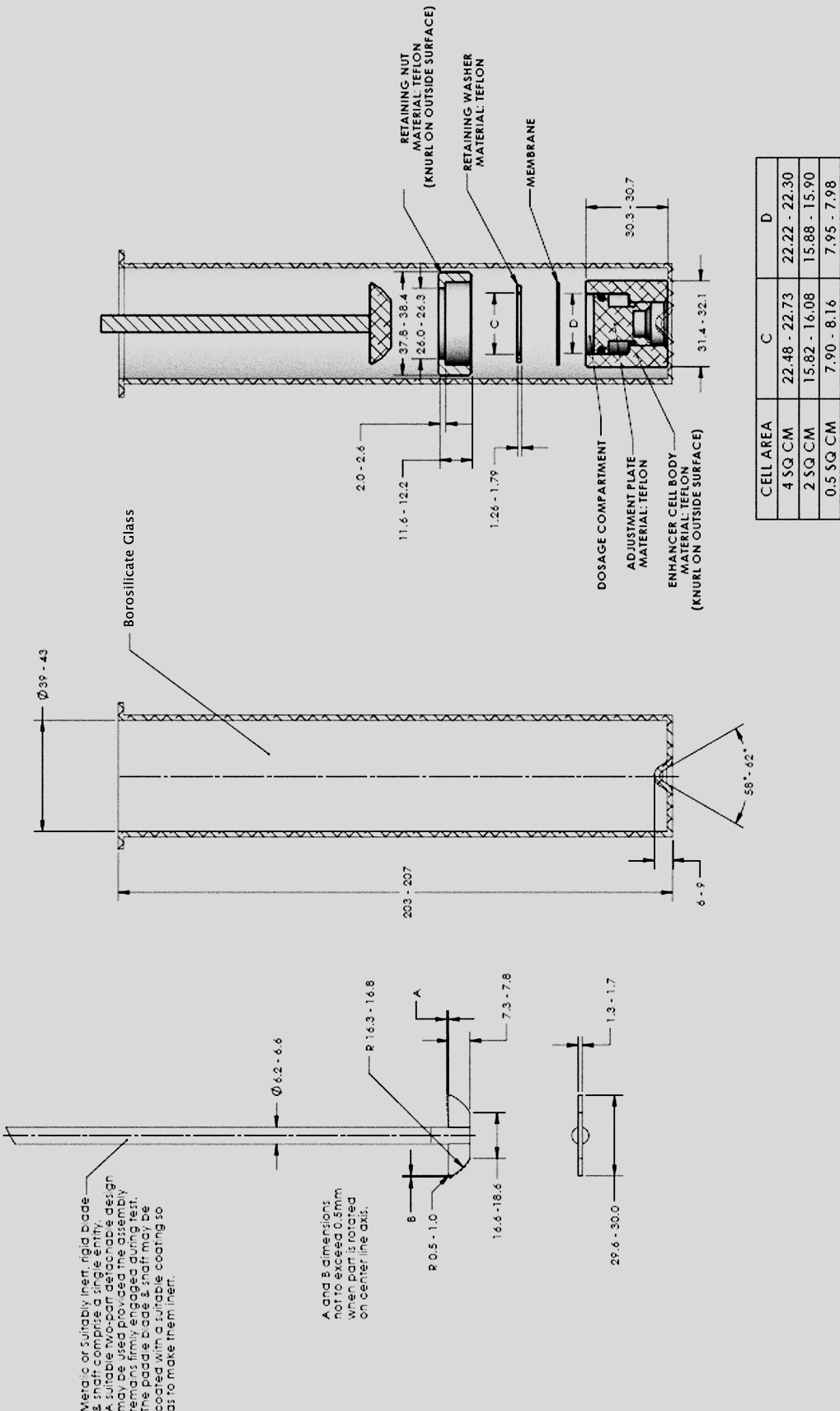


Figure 5. Immersion cell–Model A assembled in a mini vessel.

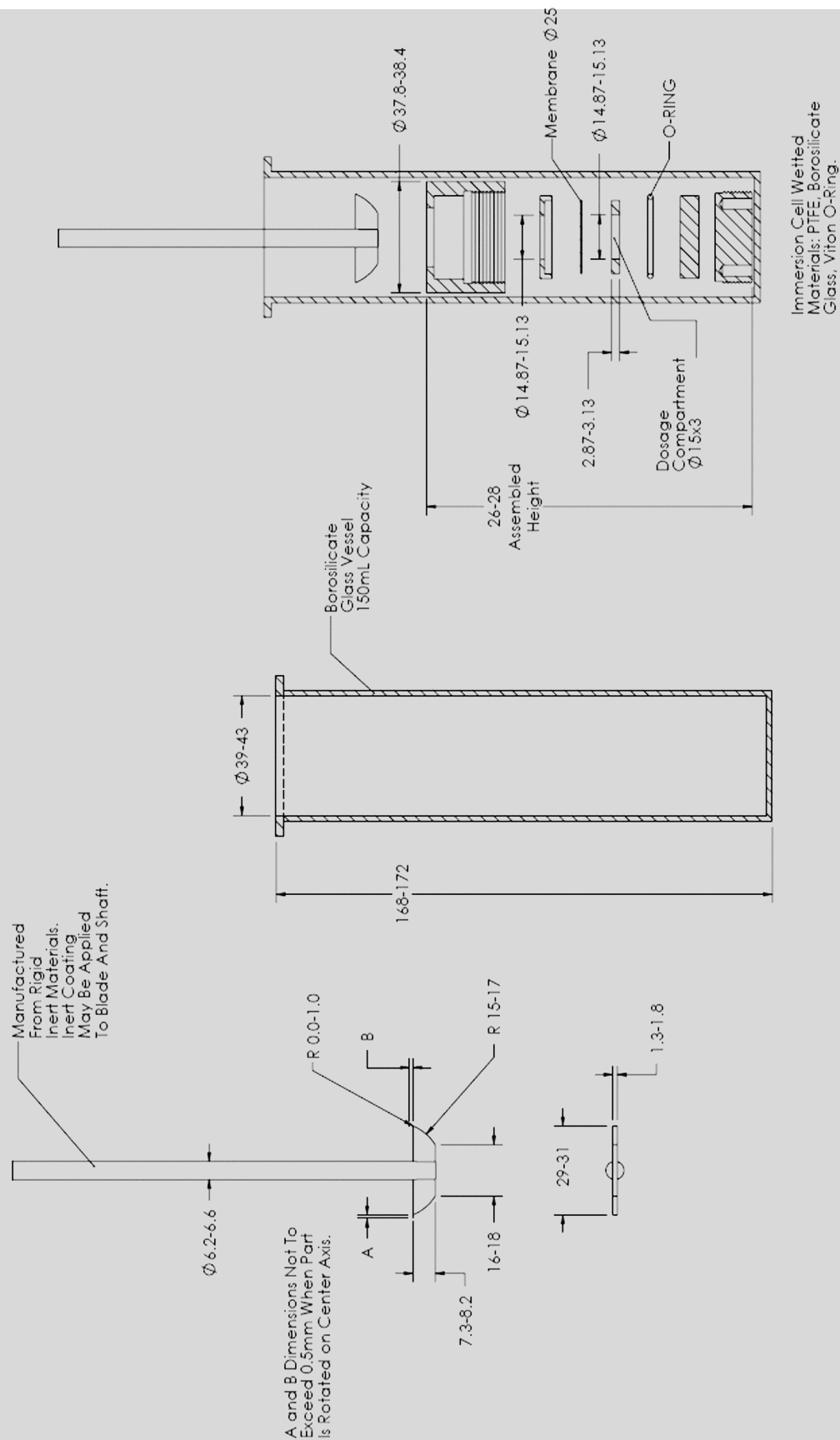


Figure 6. Immersion cell–Model B–Cell components.

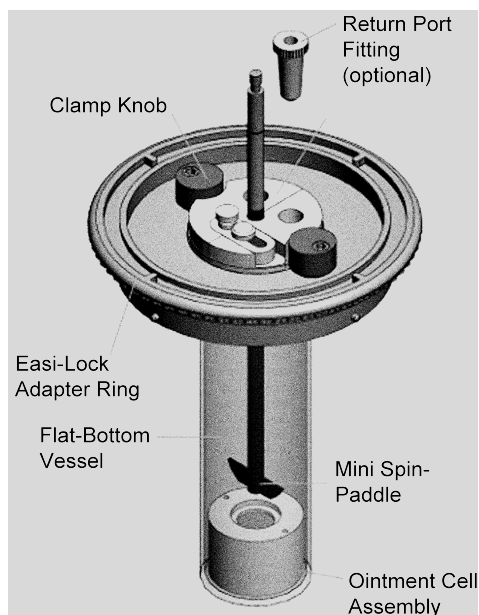


Figure 7. Immersion cell—Model B assembled in a vessel.

The immersion cell can be used with USP *Apparatus 2* (see general chapter *Dissolution* (711)) with vessel volumes that vary from 100 mL up to 4 L, but the 150- or 200-mL vessels are the most commonly used. A flat-bottom variation of the 150- or 200-mL vessel can be used to avoid the issue of dead space under the cell when it is used in a round-bottom vessel. If analysts are going to use a 150- or 200-mL vessel with USP *Apparatus 2*, then the appropriate modifications must be made, including holders for the small-volume vessels and replacement of the standard paddle with the appropriate paddle. It also may require repositioning of any automated sampling device and/or manifold. The water bath or vessel heater should be set to have the medium temperature at $32.0 \pm 0.5^\circ$ or $37.0 \pm 0.5^\circ$.

Before loading the cells and placing the medium in the vessel, set the paddle height, which is 1.0 ± 0.2 cm above the surface of the membrane. All other operational parameters, such as level, vibration, wobble, etc., should be set at the same conditions defined for USP *Apparatus 2*. The small-volume condition is qualified by first using the standard *Apparatus 2* setup and *Performance Verification Test, Apparatus 1 and 2* (see *Dissolution* (711)).

Cut the membrane to an appropriate size. If necessary, soak the membrane in the receptor medium for at least 30 min before loading. If the membrane is thick, a longer

soaking time period may be necessary. Prepare the immersion cell components as specified by the device manufacturer.

Fill the reservoir dosage area with the sample under test. Ensure that the reservoir is filled to the top in order to minimize the possibility of air bubble formation between the surface of the sample and the membrane. A uniform surface can be obtained with the aid of a spatula. The typical quantity of sample is between 300 mg and 2 g, depending on the type of immersion cell used. An excess of sample is needed to obtain a steady-state drug release rate. Using forceps or tweezers, remove the membrane from the soaking medium and place it over the top of the sample compartment. Ensure that the membrane is free of wrinkles. Assemble the immersion cell components as specified by the device manufacturer. Carefully place the completed assembly into the bottom of the dissolution vessel with the membrane facing up. The appropriate preheated medium may be preloaded in the vessel or can be added after immersion of the immersion cell to start the test. Samples from at least 5 time points should be obtained in the steady-state (linear) portion of the drug release profile. The data points are cumulative and expressed as concentration per surface area, typically per cm^2 , as a function of the square root of time. Sampling is generally performed over a 4–6 h time period. The slope of the line is the in vitro release rate of drug from the product. At the end of the test period, dismantle the cell and examine the contents for anything unusual that could explain any anomalous data (e.g., leaks, bubbles, etc.).

QUALIFICATION

USP *Apparatus 2* should be qualified according to the procedure described in *Dissolution* (711).

Drug Release Determination Using USP Apparatus 4 (Flow-Through Cell)

The adapter for semisolid dosage forms (see Figure 8) is used with the 22.6-mm cell of USP *Apparatus 4* described in *Dissolution* (711). The adapter consists of a reservoir and a ring to hold the membrane. The reservoir is available in different sizes that can accommodate from 400 to 1200 μL of product. The use of the USP *Apparatus 4* cells ensures control of temperature and hydrodynamics. The temperature can be maintained either at $32.0 \pm 0.5^\circ$ or $37.0 \pm 0.5^\circ$, depending on the intended site of the administration of the formulation. The flow rate should comply with the requirements of *Dissolution* (711) with a sinusoidal flow profile with a pulsation of 120 ± 10 pulses/min and a precision of $\pm 5\%$ of the nominal flow rate.

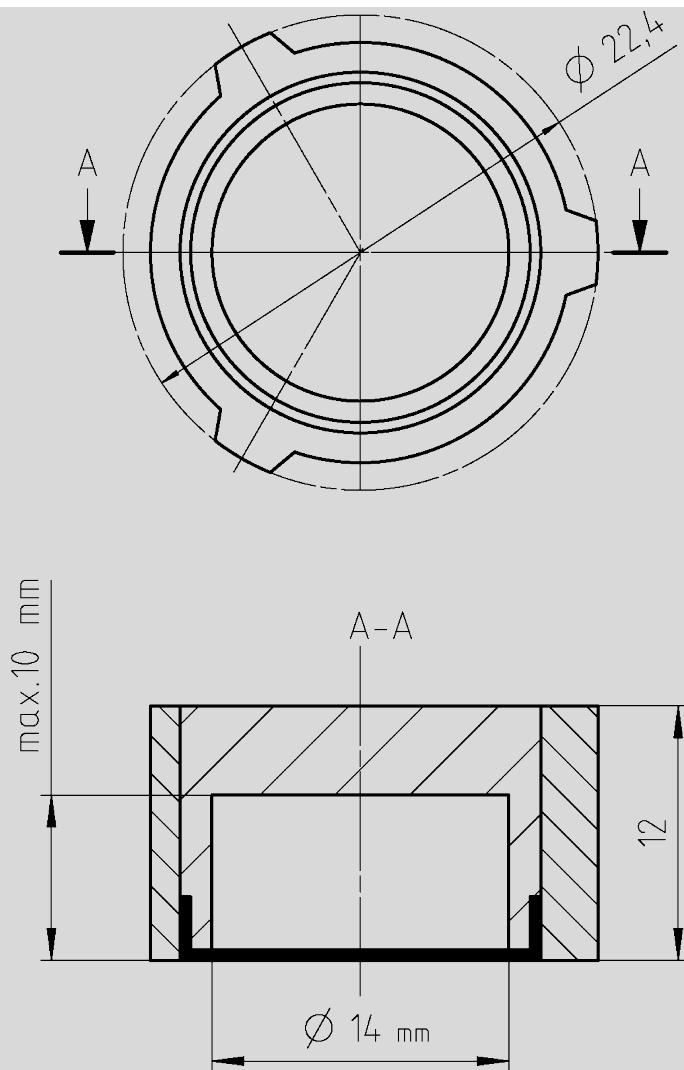


Figure 8. Adapter for topical dosage forms in USP Apparatus 4 (All dimensions are in mm).

Procedure

The membrane, which may be soaked in the receptor medium beforehand, is loaded in the membrane ring using the provided tool. The membrane should be large enough to overlap the top edge of the reservoir body with a diameter of 18 mm. The sample is loaded into the reservoir. The other side of the tool can be used to hold the reservoir while loading the sample. If necessary, the excess of sample can be removed using a spatula. Screw the membrane ring

onto the sample reservoir. Ensure that the membrane is free of wrinkles while screwing.

Remove the semisolid sample adapter from the tool, and slide it into the cylindrical part of the 22.6-mm cell with the membrane facing downward. Vertical positioning within the cell can be adjusted using the tablet holder scoring, if desired (see Figure 9). If the lower position is chosen, release can be higher due to the proximity to the flow inlet. The system is typically configured as a closed system (see Figure 10), but in some cases, an open system can be used. The prepared cell is inserted in a heating jacket.

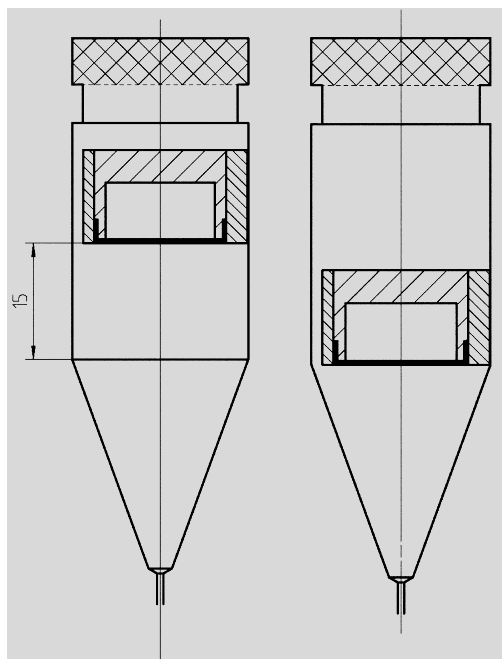


Figure 9. Vertical positioning of the insert using the tablet holder scoring (all dimensions are in mm).

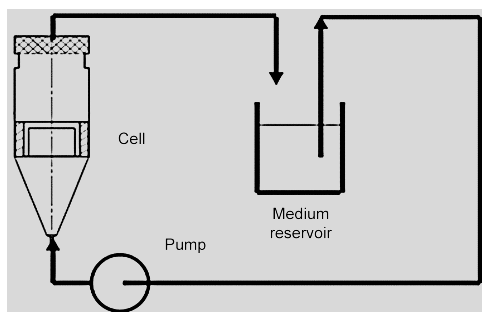


Figure 10. Closed system configuration.

The defined volume of release medium is introduced in the reservoir. Unless otherwise specified, the medium should be deaerated in order to minimize the risk of air bubbles. A deaeration procedure is described in *Dissolution* (711), but other validated deaeration techniques can be used. The reservoir can be adapted to the volume needed in order to achieve sink conditions and to ensure precision of the analytical method. Typical volumes range from 50 to 1000 mL, but values above and below this range also can be used as the formulation demands.

When the pump is switched on, the medium will be pumped through the cell. This represents the time zero of the test. Typical flow rates are 16 mL/min and 24 mL/min, but flow rate is a method-development parameter and must be optimized accordingly. The flow passing through the cell ensures both agitation and renewal of the receptor medium at the interface with the membrane.

Sampling can be performed either manually or automatically directly from the medium reservoir, thus ensuring no interference with the flow cell and its contents. An auto-

rated fraction collector may be appropriate for release periods longer than 6 h. After quantification, plot the amount of drug release per surface area versus the square root of time, with the slope of the line representing the *in vitro* release rate.

Calculation of Rate and Amount of Drug Released

Calculate the drug release rate using the following steps. Amount released ($\mu\text{g}/\text{cm}^2$) at a given time (t_1 , t_2 , etc.) (AR_i) is calculated for each sample:

$$\text{Amount released at } t_1 AR_1 = (A_{U1}/A_s) \times C_s \times 1000 \times (V_c/A_o)$$

$$\text{Amount released at } t_2 AR_2 = (A_{U2}/A_s) \times C_s \times 1000 \times (V_c/A_o) + [AR_1 \times (V_s/V_c)]$$

$$AR_n = (A_{Un}/A_s) \times C_s \times 1000 \times (V_c/A_o) + \left[(V_s/V_c) \times \sum_{i=1}^{n-1} \left(\frac{A_{U(n-1)}}{A_s} \right) \times C_s \times 1000 \times V_c/A_o \right]$$

AR = amount of drug released ($\mu\text{g}/\text{cm}^2$)

A_U = response (e.g., peak area, or peak height or absorbance) from the *Sample solution*

A_s = average response (e.g., peak area, or peak height or absorbance) from the *Standard solution*

C_s = concentration of the *Standard solution* (mg/mL)

V_c = volume of the diffusion cell (mL)

A_o = area of the orifice (cm^2)

V_s = volume of sample taken (mL)

For each cell, the individual amount of drug released is plotted versus the square root of time. The slope of the resulting line is the rate of drug release. The average of 6 slopes for each test and reference products represents the drug release rate of the dosage form, and serves as the standard for the drug product.

Application of Drug Release

The product performance test can be used to assess sameness of the drug product after post-approval changes. Because common testing artifacts, such as air bubbles and membrane defects, yield measurements that are not normally distributed, a nonparametric statistical technique is used to evaluate the test results. The Mann-Whitney U test is used to calculate the 90% confidence interval for the ratio of the slopes between the test and the reference batches. This is illustrated by the following example in which the initial drug product batch is referred to as the reference batch (R) and the changed or subsequent batch is referred to as the test batch (T). The individual amounts of drug released from R is plotted versus time, and the resulting slopes are determined. Those are the reference slopes. The process is repeated for the test batch (T).

The T/R slope ratios are calculated for each test-to-reference slope. This procedure is facilitated with a table where the values for the slopes for test and reference batches are listed down the left side and across the top of the table, respectively. The T/R slope ratios are then determined. See *Table 1*.

Table 1. Comparison of Test and Reference Slopes

	RS1	RS2	RS3	RS4	RS5	RS6
TS1	TS1/RS1	TS1/RS2	TS1/RS3	TS1/RS4	TS1/RS5	TS1/RS6
TS2	TS2/RS1	TS2/RS2	TS2/RS3	TS2/RS4	TS2/RS5	TS2/RS6
TS3	TS3/RS1	TS3/RS2	TS3/RS3	TS3/RS4	TS3/RS5	TS3/RS6
TS4	TS4/RS1	TS4/RS2	TS4/RS3	TS4/RS4	TS4/RS5	TS4/RS6
TS5	TS5/RS1	TS5/RS2	TS5/RS3	TS5/RS4	TS5/RS5	TS5/RS6
TS6	TS6/RS1	TS6/RS2	TS6/RS3	TS6/RS4	TS6/RS5	TS6/RS6

After the *T/R* ratios have been calculated, they are ordered from the lowest to the highest. The 8th and 29th *T/R* ratios are identified and converted to percent (multiplied by 100). These values represent the 90% confidence interval for the ratio of test to reference release rates. To pass first stage testing, those ratios must be within the range of 75%–133.33%.

If the results do not meet this criterion, four additional tests of 6 cells should be performed, resulting in 12 addi-

tional slope determinations for each product tested. The *T/R* slope ratios for all 18 slopes for each product tested are determined. All 324 individual *T/R* slope ratios are ordered from the lowest to the highest. To pass this second stage testing, the 110th and 215th slope ratios, representing the 90% confidence interval, must be within the range of 75%–133.33%.

■1S (USP36)

Dietary Supplements

General Chapters Information

(2021) MICROBIAL ENUMERATION TESTS— NUTRITIONAL AND DIETARY SUPPLEMENTS

INTRODUCTION

This chapter provides tests for the estimation of the number of viable aerobic microorganisms present in nutritional supplements of all kinds, from raw materials to the finished forms. Alternative methods may be substituted for the tests, provided that they have been properly validated as giving equivalent or better results. In preparing for and in applying the tests, observe aseptic precautions in handling the specimens. The term “growth” is used in a special sense herein, i.e., to designate the presence and presumed proliferation of viable microorganisms.

Change to read:

PREPARATORY TESTING

The validity of the results of the tests set forth in this chapter rests largely upon the adequacy of a demonstration that the test specimens to which they are applied do not, of themselves, inhibit the multiplication, under the test conditions, of microorganisms that may be present. Therefore, preparatory to conducting the tests on a regular basis and as circumstances require subsequently, inoculate diluted specimens of the material to be tested with separate viable cultures of the challenge microorganisms.

For the *Soybean–Casein Digest Agar Medium* used for *Total Aerobic Microbial Count*, inoculate duplicate plates with 25–250 cfu of *Staphylococcus aureus* (ATCC¹ No. 6538), *Escherichia coli* (ATCC No. 8739), and *Bacillus subtilis* (ATCC No. 6633) to demonstrate a greater than 70% bioburden recovery in comparison to a control medium. For the *Sabouraud Dextrose Agar Medium* used for *Total Combined Molds and Yeasts Count*, inoculate duplicate plates with 25–250 cfu of *Candida albicans* (ATCC No. 10231) and *Aspergillus brasiliensis* (USP36) (ATCC No. 16404) to demonstrate a greater than 70% bioburden recovery in comparison to a control medium.

¹ Available from ATCC, 10801 University Boulevard, Manassas, VA 20110-2209. Equivalent microorganisms, provided that they are from a national collection repository, can be used in lieu of ATCC strains. However, the viable microorganisms used in the test must not be more than five passages removed from the original ATCC or national collection culture.

son to a control medium. For *Enterobacterial Count (Bile-Tolerant Gram-Negative Bacteria)*, appropriate dilutions of *Escherichia coli* (ATCC No. 8739) and *Salmonella typhimurium* (ATCC No. 13311) are used. Failure of the organism(s) to grow in the relevant medium invalidates that portion of the examination and necessitates a modification of the procedure by (1) an increase in the volume of diluent, the quantity of test material remaining the same, or by (2) the incorporation of a sufficient quantity of suitable inactivating agent(s) in the diluents, or by (3) an appropriate combination of modifications to (1) and (2) so as to permit growth of the inoculum.

The following are examples of ingredients and their concentrations that may be added to the culture medium to neutralize inhibitory substances present in the sample: soy lecithin, 0.5%; and polysorbate 20, 4.0%. Alternatively, repeat the test as described in the preceding paragraph, using *Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium* to demonstrate neutralization of preservatives or other antimicrobial agents in the test material. Where inhibitory substances are contained in the product and the latter is soluble, a suitable, validated adaptation of a procedure set forth under *Procedure* using the *Membrane Filtration Method* may be used.

If, in spite of the incorporation of suitable inactivating agents and a substantial increase in the volume of diluent, it is still not possible to recover the viable cultures described above, and where the article is not suitable for the employment of membrane filtration, it can be assumed that the failure to isolate the inoculated organism is attributable to the bactericidal or bacteriostatic activity of such magnitude that treatments are not able to remove the activity. This information serves to indicate that the article is not likely to allow proliferation or contamination with the given species of microorganism. Monitoring should be continued in order to determine the inhibitory range and bactericidal activity of the article.

Change to read:

BUFFER SOLUTION AND MEDIA

Culture media may be prepared as follows, or dehydrated culture media may be used provided that, when reconstituted as directed by the manufacturer or distributor, they have similar ingredients and/or yield media comparable to those obtained from the formulas given herein.

In preparing media by the formulas set forth herein, dissolve the soluble solids in the water, using heat if necessary to effect complete solution, and add solutions of hydrochloric acid or sodium hydroxide in quantities sufficient to yield the desired pH in the medium when it is ready for use. Determine the pH at $25 \pm 2^\circ$.

Where agar is called for in a formula, use agar that has a moisture content of NMT 15%. Where water is called for in a formula, use *Purified Water*.

pH 7.2 Phosphate Buffer

Prepare a stock solution by dissolving 34 g of monobasic potassium phosphate in about 500 mL of water contained in a 1000-mL volumetric flask. Adjust to a pH of 7.2 ± 0.1 by the addition of sodium hydroxide TS (about 175 mL), add water to volume, and mix. Dispense and sterilize. Store under refrigeration. For use, dilute the stock solution with water in the ratio of 1–800, dispense as desired, and sterilize.

Media

Prepare media for the tests as described below. Alternatively, dehydrated formulations may be used provided that, when reconstituted as directed by the manufacturer or distributor, they meet the requirements of *Growth Promotion Testing*. Unless otherwise indicated elsewhere in this chapter, media are sterilized in autoclaves using a validated process. The exposure time within the autoclave at 121° will depend on the volume of media to be sterilized. Thus, for example, a 500-mL volume would need to be autoclaved using a temperature and time relationship that will ensure that the medium has attained at least an F_0 of 12–15 in the sterilization process. However, the appropriate time and temperature duration for sterilizing prepared media at any given volume should be confirmed by a thermal penetration study using a thermocouple or thermoprobe placed within the liquid medium.

FLUID CASEIN DIGEST–SOY LECITHIN–POLYSORBATE 20 MEDIUM

Pancreatic Digest of Casein	20 g
Soy Lecithin	5 g
Polysorbate 20	40 mL
Water	960 mL

Dissolve *Pancreatic Digest of Casein* and *Soy Lecithin* in 960 mL of water, heating in a water bath at 48° – 50° for about 30 min to effect solution. Add 40 mL of *Polysorbate 20*. Mix, dispense as desired, and sterilize.

SOYBEAN–CASEIN DIGEST–AGAR MEDIUM

Pancreatic Digest of Casein	15.0 g
Papaic Digest of Soybean Meal	5.0 g
Sodium Chloride	5.0 g
Agar	15.0 g
Water	1000 mL

pH after sterilization: 7.3 ± 0.2 .

FLUID SOYBEAN–CASEIN DIGEST MEDIUM

Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose	2.5 g
Purified Water	1000 mL

Dissolve the solids in the water, heating slightly to effect a solution. Cool the solution to room temperature, and adjust the pH with 1 N sodium hydroxide so that after sterilization it will have a pH of 7.3 ± 0.2 . Filter, if necessary, and dispense into suitable containers. Sterilize at a temperature and time relationship that will ensure that the medium has attained at least an F_0 of 12–15 in the sterilization process, or by a validated filtration process.

SABOURAUD DEXTROSE–AGAR MEDIUM

Dextrose	40.0 g
Mixture of Peptic Digest of Animal Tissue and Pancreatic Digest of Casein (1:1)	10.0 g
Agar	15.0 g
Water	1000 mL

Mix, and boil to effect solution.
pH after sterilization: 5.6 ± 0.2 .

VIOLET-RED BILE AGAR WITH GLUCOSE AND LACTOSE

Yeast Extract	3.0 g
Pancreatic Digest of Gelatin	7.0 g
Bile Salts	1.5 g
Lactose	10.0 g
Sodium Chloride	5.0 g
D-Glucose Monohydrate	10.0 g
Agar	15.0 g
Neutral Red	30 mg
Crystal Violet	2 mg
Water	1000 mL

Adjust the pH so that it is 7.4 ± 0.2 after heating. Heat to boiling, but do not heat in an autoclave. Pour onto plates.

MOSSEL–ENTEROBACTERIACEAE ENRICHMENT BROTH

Pancreatic Digest of Gelatin	10.0 g
D-Glucose Monohydrate	5.0 g
Dehydrated Ox Bile	20.0 g
Monobasic Potassium Phosphate	2.0 g
Dibasic Potassium Phosphate	8.0 g
Brilliant Green	15 mg
Water	1000 mL

Suspend the solids in water, and heat to boiling for 1–2 min. Transfer 120-mL portions to 250-mL volumetric flasks or 9-mL portions to test tubes, all being capped with cotton plugs or loose-fitting caps. Heat on a steam bath for 30 min. Adjust the pH so that it is 7.2 ± 0.2 after heating.

GROWTH PROMOTION TESTING

Each lot of dehydrated medium bearing the manufacturer's identifying number or each lot of medium prepared from basic ingredients must be tested for its growth-promoting qualities. Cultures of *Staphylococcus aureus* (ATCC No. 6538), *Escherichia coli* (ATCC No. 8739), *Bacillus subtilis* (ATCC No. 6633), *Candida albicans* (ATCC No. 10231), and *Aspergillus brasiliensis* ^{1S (USP36)} (ATCC No. 16404) are used. A 10^{-3} dilution of a 24-hour broth culture of the microorganism to the first dilution (in *pH 7.2 Phosphate Buffer* or *Fluid Soybean–Casein Digest Medium*) may be used as the inocula. Serially streak plates of the media with the appro-

appropriate inocula to obtain isolated colonies to demonstrate the growth-promotion qualities of the *Soybean–Casein Digest Agar* and *Sabouraud Dextrose Agar* media. Inoculate the *Fluid Soybean–Casein Digest Medium* and *Mossel–Enterobacteriaceae Enrichment Broth* with 10–100 cfu of the appropriate challenge organisms to demonstrate their growth-promotion qualities.

SAMPLING

Provide 10-mL or 10-g specimens for the tests called for in the individual monograph.

Change to read:

PROCEDURE

Prepare the specimen to be tested by a treatment that is appropriate to its physical characteristics and that does not alter the number and kind of microorganisms originally present, in order to obtain a solution or suspension of all or part of it in a form suitable for the test procedure(s) to be carried out.

For a solid that dissolves to an appreciable extent but not completely, reduce the substance to a moderately fine powder, suspend it in the vehicle specified, and proceed as directed under *Total Aerobic Microbial Count*.

For a fluid specimen that consists of a true solution, or a suspension in water or a hydroalcoholic vehicle containing less than 30% of alcohol, and for a solid that dissolves readily and practically completely in 90 mL of *pH 7.2 Phosphate Buffer* or the media specified, proceed as directed under *Total Aerobic Microbial Count*.

For water-immiscible products, prepare a suspension with the aid of a minimal quantity of a suitable, sterile emulsifying agent (such as one of the polysorbates), using a mechanical blender and warming to a temperature not exceeding 45°, if necessary, and proceed with the suspension as directed under *Total Aerobic Microbial Count*.

Total Aerobic Microbial Count

For specimens that are freely soluble, use the *Membrane Filtration Method* or *Plate Method*. For specimens that are sufficiently soluble or translucent to permit use of the *Plate Method*, use that method; otherwise, use the *Multiple-Tube Method*. With either method, first dissolve or suspend 10.0 g of the specimen if it is a solid, or 10 mL, accurately measured, if the specimen is a liquid, in *pH 7.2 Phosphate Buffer*, *Fluid Soybean–Casein Digest Medium*, or *Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium* to make 100 mL. For viscous specimens that cannot be pipetted at this initial 1:10 dilution, dilute the specimen until a suspension is obtained, i.e., 1:50 or 1:100, etc., that can be pipetted. Perform the test for absence of inhibitory (antimicrobial) properties as described under *Preparatory Testing* before the determination of *Total Aerobic Microbial Count*. Add the specimen to the medium NMT 1 h after preparing the appropriate dilutions for inoculation.

MEMBRANE FILTRATION METHOD

Dilute the fluid further, if necessary, so that 1 mL will be expected to yield 30–300 colonies. Pipet 1 mL of the final dilution into 5–10 mL of *pH 7.2 Phosphate Buffer*, *Fluid Soybean–Casein Digest Medium*, or *Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium*. Wash each membrane with an appropriate amount of one of the above diluents. Transfer each membrane to a Petri dish containing *Soybean–Casein Digest–Agar Medium*, previously solidified at room temperature. Incubate the plates at a temperature 30°–35° for 48–72 h. Following incubation, examine the plates for growth, count the number of colonies, and express the average for the two plates in terms of the number of microorganisms per g or per mL of specimen. If no microbial colonies are recovered from the dishes representing the initial 1:10 dilution of the specimen, express the results as “less than 10 microorganisms per g or per mL of specimen”.

PLATE METHOD

Dilute the fluid further, if necessary, so that 1 mL will be expected to yield 30–300 colonies. Pipet 1 mL of the final dilution onto each of two sterile Petri dishes. Promptly add to each dish 15–20 mL of *Soybean–Casein Digest–Agar Medium*, previously melted and cooled to about 45°. Cover the Petri dishes, mix the sample with agar by gently tilting or rotating the dishes, and allow the contents to solidify at room temperature. Invert the Petri dishes and incubate for 48–72 h. Following incubation, examine the plates for growth, count the number of colonies, and express the average for the two plates in terms of the number of microorganisms per g or per mL of specimen. If no microbial colonies are recovered from the dishes representing the initial 1:10 dilution of the specimen, express the results as “less than 10 microorganisms per g or per mL of specimen”.

MULTIPLE-TUBE METHOD

Into each of 14 test tubes of similar size, place 9.0 mL of sterile *Fluid Soybean–Casein Digest Medium*. Arrange 12 of the tubes in four sets of three tubes each. Put aside one set of three tubes to serve as the controls. Into each of three tubes of one set (“100”) and into a fourth tube (A) pipet 1 mL of the solution or suspension of the specimen, and mix. Pipet 1 mL from tube A into the one remaining tube (B), not included in a set, and mix. These two tubes contain 100 mg or 100 µL and 10 mg or 10 µL of the specimen, respectively. Into each of the second set (“10”) of three tubes pipet 1 mL from tube A, and into each tube of the third set (“1”) pipet 1 mL from tube B. Discard the unused contents of tubes A and B. Close well, and incubate all of the tubes. Following incubation, examine the tubes for growth: the three control tubes remain clear, and the observations in the tubes containing the specimen, when interpreted by reference to *Table 1*, indicate the most probable number of microorganisms per g or per mL.

Table 1. Most Probable Count by Multiple-Tube Method

Observed Combinations of Numbers of Tubes Showing Growth in Each Set			Most Probable Number of Microorganisms per g or per mL
Number of mg or μ L of specimen per tube			
100	10	1	
3	3	3	M ore than 1100
3	3	2	1100
3	3	1	500
3	3	0	200
3	2	3	290
3	2	2	210
3	2	1	150
3	2	0	90
3	1	3	160
3	1	2	120
3	1	1	70
3	1	0	40
3	0	3	95
3	0	2	60
3	0	1	40
3	0	0	23
2	2	0	21
2	1	1	20
2	1	0	15
2	0	1	14
2	0	0	9
1	2	0	11
1	1	0	7
1	0	0	4
0	1	0	3
0	0	0	<3

Table 2. Most Probable Enterobacterial Count

Observed Presence of Enterobacteria			Most Probable Number of Enterobacteria per g or per mL _{1S (USP36)}
Number of g or mL _{1S (USP36)} of specimen per tube			
0.1	0.01	0.001	
+	+	+	
+	+	+	More than 10^3 _{1S (USP36)}
+	+	–	Fewer than 10^3 but more than 10^2 _{1S (USP36)}
+	–	–	Fewer than 10^2 but more than 10^1 _{1S (USP36)}
–	–	–	Fewer than 10^1 _{1S (USP36)}

Total Combined Molds and Yeasts Count

Procedure—Proceed as directed for *Membrane Filtration Method* or *Plate Method* under *Total Aerobic Microbial Count*, except to use the same amount of *Sabouraud Dextrose–Agar Medium* instead of *Soybean–Casein Digest–Agar Medium* and to incubate the plates for 5–7 days at 20°–25°.

Retest—For the purpose of confirming a doubtful result by any of the procedures outlined in the foregoing tests following their application to a 10-g specimen, a retest on an additional 10-g specimen from the original sample and a 10-g specimen from the new sample of the nutritional supplement may be conducted. Proceed as directed under *Procedure*.

Enterobacterial Count (Bile-Tolerant Gram-Negative Bacteria)

Dissolve or suspend the sample in a sufficient volume of pH 7.2 Phosphate Buffer or Fluid Soybean–Casein Digest Me-

dium and dilute with *Fluid Soybean–Casein Digest Medium* to 100 mL. Pre-incubate for 2–5 h at 20°–25° in soybean–casein digest broth diluent; inoculate suitable quantities of *Mossel–Enterobacteriaceae Enrichment Broth* to contain 0.1, 0.01, or 0.001 g or mL of the product. Incubate at 30°–35° for 24–48 h. Subculture onto a plate of *Violet-Red Bile Agar with Glucose and Lactose*, and incubate at 30°–35° for 18–24 h. Growth of well developed, generally red or reddish, colonies of Gram-negative bacteria reveal the presence of enterobacteria. Determine the most probable number of microorganisms per g or per mL by reference to *Table 2*.

(2023) MICROBIOLOGICAL ATTRIBUTES OF NONSTERILE NUTRITIONAL AND DIETARY SUPPLEMENTS

The raw materials, pharmaceutical ingredients, and active ingredients used in the manufacture of nutritional and dietary articles may range from chemically synthesized vitamins to plant extracts and animal byproducts, and these ingredients are typically not sterile. Considerable experience has accrued with these highly refined plant- and animal-derived pharmaceutical ingredients, such as microcrystalline cellulose, modified starch, lactose, and magnesium stearate, and their microbiological attributes are well established. Botanicals may be microbiologically contaminated at any point during cultivation, harvesting, processing, packing, and distribution. Major sources of microbial contamination are associated with human or animal feces used as plant manure; contaminated irrigation water and/or process water; and poor worker hygiene and sanitation practices during harvesting, sorting, processing, packaging, and transportation. Furthermore, it is essential that microbiological contamination be minimized during the manufacture of nonsterile dietary supplements. To achieve this, Good Manufacturing Practices are employed and adequate microbiological specifications are established.

Microbiological process control, control of the bioburden of raw materials, and control of the manufacturing process to minimize cross-contamination are necessary to guarantee acceptable microbial quality in the final dosage forms. Because nonaqueous or dry dosage forms do not support microbial growth because of low water activity, the microbial quality of such articles is a function of the microorganisms introduced through ingredients or during processing. In addition to considering the intended use of the product, the frequency of microbial testing for the finished nonsterile dietary supplement would be a function of the historical microbial testing database of that product, knowledge of the manufacturing processes, the susceptibility of the formulation to microbial proliferation, and the demonstrated effectiveness of programs controlling the raw materials.

FORMULATION AND PROCESS DESIGN

From a microbiological perspective, the development of the formulation of nutritional or dietary supplements includes an evaluation of raw materials and their suppliers and the contribution made to the products by each ingredient and the manufacturing processes. Characterization of these elements allows the adequacy of the manufacturing process to be demonstrated. For example, if a product is formulated with an ingredient of botanical or animal origin known to possess a high, variable, or unpredictable level of microbiological contamination, it is necessary to ensure that the microbiological monitoring identifies ingredients that have an inappropriate bioburden level and that a premanufacturing process such as drying, extraction, heat treatment, irradiation, or gaseous sterilization treatment will inactivate or remove any objectionable contaminant possibly present.

However, the selected treatment technique should not have any adverse effects. The treatment of raw materials by irradiation and ethylene oxide may cause unwanted changes affecting the safety and efficacy of the raw material. For instance, when treated by ethylene oxide, crude extracts containing alkaloids have shown reduced contents of alkaloids. Dry heat treatment has been used for inactivation as well, but requires further evaluation because it may ad-

versely affect stability and degradation of the raw material. With regard to the design of the manufacturing process, appropriate consideration should be given to the microbiological effect of wet granulation manufacturing processes. Wetting of a dry powder can result in increased levels of microorganisms if the granulation is stored prior to drying. However, it is recognized that the pressure and temperature associated with compression of tablets will decrease microbial counts. Antimicrobial activity is also achieved, especially with aqueous preparations, by the addition of chemicals that have known antimicrobial properties and that are compatible with the formulation.

However, antimicrobial preservation is not a substitute for Good Manufacturing Practices. A process has to be designed to minimize the microbiological population. Operating procedures, temperatures, and time limits, including holding times, are established to protect the product from microbiological contamination and growth. All processes have to be validated for their intended purposes. Moreover, in-process manufacturing and testing controls necessary for microbiological quality should be identified and implemented.

FACILITIES, EQUIPMENT, WATER, AND SANITIZATION

Facilities—The facilities, including the building and the heating, ventilation, and air-conditioning (HVAC) systems, should be designed to minimize microbiological contamination. The design of facilities used for the manufacture of supplements and their operating parameters should be documented, and the documentation should include, when appropriate, HVAC filter types, space pressure differentials, temperature, and relative humidity and air changes. Dry products processed in a dry environment do not possess a high potential for increased microbial levels. However, some control is warranted to minimize microbiological and chemical contamination. Potentially problematic areas are those that utilize *Purified Water* for wet granulation, batching liquid products, and film-coating tablets, because water encourages microbial growth.

Equipment—Equipment used for the processing of semi-solid and dry supplements should be designed to promote sanitary conditions, to be self-drying, and to be easy to clean. Dryers, ovens, wet granulation equipment, bulk tanks, and equipment for preparation of coating solutions are periodically evaluated to ensure that cleaning procedures are adequate.

Water—As one of the major components in nutritional and dietary supplement manufacturing processes, water deserves a special consideration in the microbiological control of these articles. It is a growth medium for a variety of microorganisms that present a threat to product quality, safety, preservation, and stability. Water may even act as a carrier of objectionable microorganisms. In view of this, water used in manufacturing is *Purified Water*. For the manufacture of raw materials, process water that meets specific microbiological objectives and U.S. Environmental Protection Agency National Drinking Water standards or equivalent European and Japanese standards may be used.

Cleaning and Sanitization—Detailed and specific cleaning and sanitization procedures should be evaluated, developed, and validated, with special attention given to product contact surfaces. Personnel should possess sufficient knowledge of these procedures.

SUPPLEMENT COMPONENTS

Raw materials, excipients, and active substances as components of nutritional and dietary supplements can be a primary source of microbiological contamination. Specifications should be developed and sampling plans and test proce-

dures should be employed to guarantee the desired microbiological attributes of these materials. The nature and extent of microbiological testing should be based upon a knowledge of the material’s origin, its manufacturing process, use, historical data, and experience. For instance, materials of animal or botanical origin that are not highly refined might require special, more frequent testing than synthetic products.

Since members of the family Enterobacteriaceae are a major component of the normal epiphytic and endophytic microflora (e.g., members of genera *Klebsiella*, *Enterobacter*, and *Erwinia*) and have been associated with the seeds, pods, roots, leaves, and stems of plants of economic importance, coliform or Enterobacteriaceae counts will not be an appropriate general microbiological criterion for botanicals. However, when it is considered advantageous, coliform or Enterobacteriaceae counts may be included in the individual monographs. Typically on new leaves, bacteria predominate in the microflora, while yeast and filamentous fungi succeed bacteria and become dominant late in the growing season. With dried botanicals, the bacterial population will tend to change from Gram-negative bacteria to Gram-positive spore formers and fungi. Refinement of botanicals from chopped or powdered plant material to powdered extracts using alcoholic, alkaline, acid hydro-alcoholic, or aqueous extracting materials will reduce the likelihood of vegetative microorganisms within the botanical material. The classification of botanical materials is contained in *Table 1*.

Change to read:

MICROBIOLOGICAL TESTING

Frequency of Sampling and Testing

Microbiological attribute sampling and testing plans vary widely. In some cases, no sampling or testing is necessary; in other cases, periodic monitoring is warranted; and yet for some articles, each batch requires sampling and testing. The design of the sampling and testing plans and the kind of attributes examined depend on the application and the type of the product, the potential for contamination from components and processing, the growth promotion or inhibition properties of the formulation, and the target population for the supplement. For example, a powdered botanical may have highly variable microbiological attributes so that an incoming batch would be sampled and composite testing would not be advised, while a highly refined botanical extract may not require routine microbial testing. Similarly, products with a low water activity will not be susceptible to microbial growth during their shelf life provided they are protected from elevated humidity by their containers.

Microbial Enumeration Tests

See the *Introduction* under *Microbial Enumeration Tests—Nutritional and Dietary Supplements* (2021). These tests provide meaningful information regarding the microbiological acceptability of excipients, active substances, and nonsterile supplement formulations. If the individual monograph does not specify microbial enumeration limits, the guidance provided in this chapter is used. Acceptable general limits of microbial levels for raw materials, excipients, and botanical products are shown in *Table 2*; and those for raw materials, excipients, active ingredients, and other nonsterile finished articles that are nutritional supplements, but do not contain botanicals, are shown in *Table 3*.

Table 1. Definitions of a Range of Botanical Materials

Botanical Preparation	Definition
Chopped or Powdered Botanicals	Hand-picked portions of the botanical (e.g., leaves, flowers, roots, tubers, etc.) that are air dried, chopped, flaked, sectioned, ground, or pulverized to the consistency of a powder.
Botanical Extracts	Extracts are solids or semisolid preparations of a botanical that are prepared by percolation, filtration, and concentration by evaporation of the percolate. The extracting material may be alcoholic, alkaline, acid hydro-alcoholic, or aqueous in nature. Typically, an extract is 4–10 times as strong as the original botanical. The extracts may be semisolids or dry powders termed powdered extracts.
Tinctures	Tinctures are solutions of botanical substances in alcohol obtained by extraction of the powdered, flaked, or sectioned botanical.
Infusions	Infusions are solutions of botanical principles obtained by soaking the powdered botanical in hot or cold water for a specified time and straining. Typically, infusions are 5% in strength.
Decoctions	Decoctions are solutions of botanicals prepared by boiling the material in water for at least 15 min and straining. Typically, decoctions are 5% in strength.
Fluidextracts	A fluidextract is an alcoholic liquid extract made by percolation of a botanical so that 1 mL of the fluidextract represents 1 g of the botanical.
Botanicals to be treated with boiling water before use	Dried botanicals to which boiling water is added immediately prior to consumption.

Table 2. Recommended Microbial Limits for Botanical Ingredients and Products

Material	Recommended Microbial Limit Requirements (cfu/g or mL)
Dried or Powdered Botanicals	Total aerobic microbial count NMT 10 ⁵
	Total combined yeasts and molds count NMT 10 ³
	Bile-tolerant Gram-negative bacteria NMT 10 ³
	Absence of <i>Salmonella</i> spp. and <i>E. coli</i> in 10 g
Powdered Botanical Extracts	Total aerobic microbial count NMT 10 ⁴
	Total combined yeasts and molds count NMT 10 ³
	Absence of <i>Salmonella</i> spp. and <i>E. coli</i> in 10 g
Tinctures	Total aerobic microbial count NMT 10 ⁴
	Total combined yeasts and molds count NMT 10 ³
Fluid extracts	Total aerobic microbial count NMT 10 ⁴
	Total combined yeasts and molds count NMT 10 ³
Infusions/Decoctions	Total aerobic microbial count NMT 10 ²
	Total combined yeasts and molds count NMT 10
Nutritional Supplements with Botanicals	Total aerobic microbial count NMT 10 ⁴
	Total combined yeasts and molds count NMT 10 ³
	Absence of <i>Salmonella</i> spp. and <i>E. coli</i> in 10 g
Botanicals to be treated with boiling water before use	Total aerobic microbial count NMT 10 ⁶ 1S (USP36)
	Total combined yeasts and molds count NMT 10 ⁴ 1S (USP36)
	Bile-tolerant Gram-negative bacteria NMT 10 ² 1S (USP36)
	Absence of <i>E. coli</i> and <i>Salmonella</i> spp. 1S (USP36) in 10 g

Table 3. Recommended Microbial Limits for Dietary Supplement Ingredients and Products

Material	Recommended Microbial Limit Requirements (cfu/g or mL)
Other raw materials and dietary supplement ingredients	Total aerobic microbial count NMT 10 ³
	Total combined yeasts and molds count NMT 10 ²
	Absence of <i>E. coli</i> in 10 g
Nutritional supplements with synthetic or highly refined ingredients	Total aerobic microbial count NMT 10 ³
	Total combined yeasts and molds count NMT 10 ²
	Absence of <i>E. coli</i> in 10 g

Absence of Objectionable Microorganisms

See Introduction under Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements (2022). Absence of one or more species of objectionable microorganisms is required in some individual monographs.

Test for Aflatoxins—Dietary and nutritional articles containing botanical products with a history of mycotoxin contamination are also typically tested for aflatoxins, especially if the material is obtained from roots or rhizomes. See Articles of Botanical Origin (561) for the details of a test for aflatoxins. Where necessary, this test is included in the individual monograph.

Solid Oral Dosage Forms—Among all dosage forms, solid oral dosage forms present the lowest microbiological risk because of their method of manufacture, low water activity, and route of administration. When justified, reduced microbiological testing may be appropriate.

Other Concerns—The presence of some microorganisms in articles can be an indicator of processes that are not under microbiological control. For example, Purified Water used at some stage of the manufacture of these products might contain a typical flora of Gram-negative microorgan-

isms. As with pharmaceutical products, inadequate processing of water and poor maintenance of water systems may result in the contamination of processed formulations by Gram-negative microorganisms.

Add the following:

(2232) ELEMENTAL CONTAMINANTS IN DIETARY SUPPLEMENTS

The objective of this general chapter is to limit the amounts of elemental contaminants in finished dietary supplement dosage forms labeled as conforming to USP or NF standards. This general chapter is not intended to set limits for dietary ingredients. Those limits are set in the corresponding individual monographs.

The focus of this general chapter is on the four major elements of toxicological concern: arsenic, cadmium, lead, and mercury. The extent of testing can be determined using a risk-based approach that takes into account the likelihood of contamination. Manufacturers should consider the presence of unexpected elemental contaminants to determine compliance.

LIMITS OF ELEMENTAL CONTAMINANTS

The levels of elemental contaminants should be restricted as shown in Table 1 unless otherwise stated in the individual monograph. Specific monographs may provide different limits for articles that need to be consumed in large quantities.

Table 1

Element	PDE ($\mu\text{g/day}$) ^a
Arsenic (inorganic)	15
Cadmium	5
Lead	10
Mercury (total)	15
Methylmercury (as Hg)	2

^a Permitted Daily Exposure (PDE) is derived from the Provisional Tolerable Weekly Intake (PTWI) that is recommended by the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) by subtracting the daily exposure ($\mu\text{g/day}$) to each elemental contaminant from air, food, and drinking water. A body weight of 50 kg and a safety factor are used to calculate the PDE. Other regulations (i.e.: Proposition 65 in California) may require different limits; manufacturers are responsible for compliance with applicable local requirements differing from these PDE values.

Arsenic may be measured using a nonspeciation procedure under the assumption that all arsenic contained in the supplement is in the inorganic form. Where the limit is exceeded using a nonspeciation procedure, compliance with the limit for inorganic arsenic shall be demonstrated on the basis of a speciation procedure. Methylmercury determination is not necessary when the content for total mercury is less than the limit for methylmercury.

OPTIONS FOR COMPLIANCE WITH THE LIMITS OF ELEMENTAL CONTAMINANTS

In order for a dietary supplement finished dosage form to comply with the limits for elemental contaminants as described in this chapter, the level of elemental contaminant in the finished dietary supplement should be NMT the PDE. The following three options are available for determining compliance with the limits for elemental contaminants in dietary supplements.

Dietary Supplement Analysis Option

This option is generally applicable. In this option the finished dietary supplement dosage form is analyzed according to the procedures in the general chapter *Elemental Impurities—Procedures* (233) or the speciation procedures given in this chapter. The results obtained from the analysis of a typical serving size, scaled to a maximum daily intake, are compared to the PDE, as stated in *Table 1*.

Analysis: Proceed as directed below in this chapter. Calculate the measured amount of each elemental contaminant, in $\mu\text{g/day}$ intake, as:

$$\text{Result} = \text{MVSS} \times N$$

MVSS = measured amount of each elemental contaminant ($\mu\text{g/serving size}$)
 N = maximum daily intake of the supplement recommended in the labeling (servings/day)

Acceptance criteria: The measured amount/daily intake is NMT the PDE value given in *Table 1*.

Individual Component Option

This option is applicable to finished dietary supplement dosage forms with a maximum daily intake of NMT 10 g of the dietary supplement finished product.

Analysis: Unless otherwise specified in the individual monograph, proceed with the individual ingredient as directed below in this chapter.

Acceptance criteria: The product meets the requirements when each component used to prepare the finished dietary supplement meets the limits given in *Table 2*.

Table 2

Element	Individual Component Limits ($\mu\text{g/g}$) ^a
Arsenic (inorganic) ^b	1.5
Cadmium	0.5
Lead	1.0
Mercury (total)	1.5
Methylmercury (as Hg) ^c	0.2

^a The limits for individual components are based on a maximum daily intake of 10 g of a dietary supplement and are intended for use only with *Options for Compliance with Limits of Elemental Contaminants, Individual Component Option*.

^b Arsenic may be measured using a nonspeciation procedure under the assumption that all arsenic contained in the supplement is in the inorganic form. Where the limit is exceeded using a nonspeciation procedure, compliance with the limit for inorganic arsenic shall be demonstrated on the basis of a speciation procedure.

^c Methylmercury determination is not necessary when the content for total mercury is less than the limit for methylmercury.

[NOTE—If all components in a formulation meet the limits given for the *Individual Component Limits*, these components can be used in any proportion. No further calculation is necessary.]

Summation Option

This option can be used for finished dietary supplement dosage forms that are consumed in quantities greater than 10 g/day or where the acceptance limit for any contaminant in any component of the dietary supplement exceeds the applicable *Individual Component Limit*.

Analysis: Unless otherwise specified in the individual monograph, proceed with the individual ingredient as directed below in this chapter.

Calculate the amount of each elemental contaminant, in $\mu\text{g/day}$ intake, present in the finished dietary supplement dosage form:

$$\text{Result} = \Sigma(C_i \times W_i) \times N$$

C_i = elemental contaminant concentration in the individual component ($\mu\text{g/g}$)
 W_i = weight of each individual component per serving of the dietary supplement (g/serving)
 N = maximum daily intake of the supplement recommended in the labeling (servings/day)

Acceptance criteria: The calculated amount of each elemental contaminant/daily intake is NMT the PDE value given in *Table 1*.

ANALYTICAL PROCEDURES FOR TOTAL ELEMENTAL CONTAMINANTS

Performance-based methodology for analysis of total elemental contaminants in general chapter *Elemental Impurities—Procedures* (233) is applicable for dietary supplements. The validation necessity will vary depending on the situation. In all three options described in the section *Options for Compliance with the Limits of Elemental Contaminants*, the use of *Validation of Limit Procedures* (see *Elemental Impurities—Procedures* (233)) may be appropriate. However, for the *Summation Option*, acceptable levels of validation must be determined on a case-by-case basis. Validation of a procedure using the *Validation of Quantitative Procedures* (see *Elemental Impurities—Procedures* (233)) is acceptable for all options under all circumstances and is generally preferred.

The determination of the level of validation necessity is at the discretion of the manufacturer and the competent regulatory authority.

Analytical Procedure for Inorganic Arsenic

Where the level of total arsenic exceeds the limit recommended in this chapter, speciation may be used to determine the amount of inorganic arsenic present. The following procedure is suggested for determination of inorganic arsenic, but any validated procedure shown to give equivalent or better results can be used.

Apparatus

Figure 1

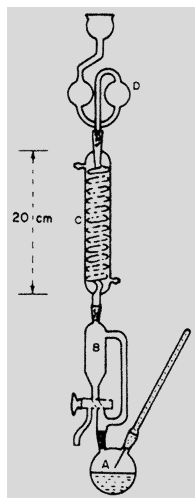


Figure 1. Special apparatus for the determination of inorganic arsenic (A, 250-mL distillation flask; B, receiver chamber, approximately 50-mL capacity; C, reflux condenser; D, splash head or security funnel).

Reagents

Distillation-reducing solution: 72 mg/mL of ACS-grade, low-arsenic, ferrous chloride tetrahydrate ($\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$) in 6.6 N hydrochloric acid. [NOTE—Prepare fresh on the day of use.]

Control: 6.0 μg of As (6.0 mL of *Standard Arsenic Solution*). [NOTE—Use this amount rather than the 3.0 mL specified for *Standard Preparation* in the general chapter *Arsenic* (211), *Method I*.]

Sample solution: Take a 2.00-g sample that has previously been ground to pass through a 60-mesh screen, and transfer to a distillation flask (A). To the flask add 50 mL of *Distillation-reducing solution*, connect the flask to the receiver chamber (B), complete the assembly of the apparatus, and begin circulating tap water through the condenser (C). Half-fill the lower two bulbs of the splash head (D) with water. Maneuver the stopcock to cause the contents of the receiver chamber to drain into the distillation flask, heat the flask until the temperature above the solution reaches $106^\circ\text{--}108^\circ$, and continue refluxing at this temperature for 45 min. Close the stopcock, continue heating at $108^\circ\text{--}110^\circ$, and collect 30–33 mL of distillate in the receiver chamber. Remove the heating source, and allow the temperature to drop to about 80° .

Drain the distillate from the receiver chamber into a 250-mL beaker that is contained in an ice-water bath. Close the stopcock, and add a second 50-mL portion of the *Distillation-reducing solution* through the thermometer opening to

the distillation flask. Replace the thermometer, increase the temperature to $108^\circ\text{--}110^\circ$, and collect a second 30–33-mL portion of distillate in the receiver chamber.

Drain the second distillate into the beaker containing the first portion, and continue cooling in the ice-water bath until the combined distillate cools to room temperature. Remove the splash head, and wash its contents into the beaker. Also, wash down the inside of the condenser and receiver chamber with water, collecting the washings in the beaker. Pass the beaker contents through a Whatman No. 40, or equivalent, filter paper, collecting the filtrate in a 300-mL Erlenmeyer flask having a 24/40 standard-taper joint, to be used later as an arsine generator flask. Wash the filter three times with water so that the final volume of filtrate measures 200 mL.

Analysis: Add 2 mL of potassium iodide TS and 0.5 mL of stronger acid stannous chloride TS to the *Sample solution* contained in the Erlenmeyer flask, and proceed as directed in *Arsenic* (211), *Method I*, *Procedure*, beginning with “Allow to stand at room temperature for 30 minutes.”

Analytical Procedure for Methylmercury

Where methylmercury determination is required, the following procedure is suggested. However, any validated procedure shown to give equivalent or better results can be used.

Apparatus

NOTE—Wash all glassware with a laboratory detergent, and rinse thoroughly with hot tap water followed by purified water. Rinse with acetone, and let dry.

The system consists of an HPLC connected through an interface to an atomic absorption detector for mercury determination at 253.7 nm with a mercury hollow-cathode lamp, deuterium background corrector, and gas flow-through cell with open ends or quartz closed ends (10–25-mm ID \times 100–115-mm).

Interface assembly (see *Figure 2*): Consists of the following components:

1. *Heater*—With 1-inch thick magnesia and alumina insulation
2. *Flowmeter*
3. *Temperature-indicating device*—Ranging from $0^\circ\text{--}1370^\circ$
4. *Short condenser*—175-mm jacket length, standard taper 24/40
5. *Rubber stopper*—No. 5, solid neoprene. [NOTE—A suitable rubber stopper is available as No. 14–141F from Fisher Scientific Co.]
6. *Stainless steel tubing*—1/16 inch (1.6 mm) OD, 0.04 inch (1 mm) ID
7. *Trap*—Test tube, 125 \times 15 mm
8. *Boiling flask*—2 neck, 500 mL. [NOTE—A suitable boiling flask is available as Kontes No. 605000.]
9. *Stainless steel tubing*—Two 6-inch (15-cm) lengths
10. *Plastic tubing*—Spaghetti type, 0.057–0.067 inch (1.45–1.7 mm) ID
11. *Plastic tubing*—Spaghetti type, as connector to AAS system
12. *Electrical connection*—Standard 120-V plug to variable voltage transformer

Atomic absorption spectrophotometer (AAS): Follow the manufacturer's operating instructions for mercury determination at 253.7 nm with deuterium background correction. Typical response for an injection of 0.100 μg Hg/100 μL standard is approximately 0.20 A using a cell of 25-mm ID \times 115-mm. Use a recording device set to obtain approximately 30%–50% full scale for an injection of 0.100 μg Hg/100 μL standard. The working range is approximately 0.01–0.25 μg Hg/100 μL injected.

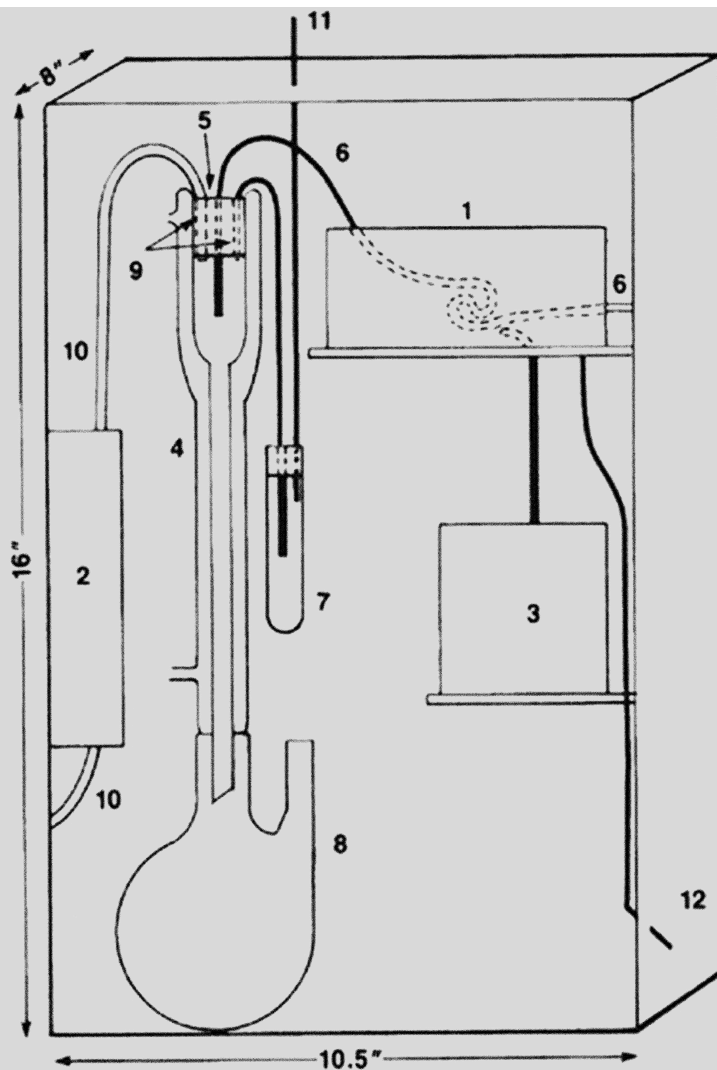


Figure 2. A diagram of the HPLC/AAS interface.

Figure 2

Reagents [NOTE—Use water double-distilled in glass.]

Sodium thiosulfate solution: Use a 0.01 M solution.

Hydrochloric acid solution: Use a 1.8 M solution.

Chromatographic siliceous earth: Acid-washed.

[NOTE—A suitable grade is available as acid-washed Celite 545.]

Methylmercuric chloride stock standard solution: Use a solution equivalent to 100 µg/mL of mercury from methylmercuric chloride prepared by dissolving 125 mg of methylmercuric chloride in 20 mL of methanol and diluting with water to 1 L.

Ammonium acetate solution: Use a 0.05 M solution.

Mobile phase: Methanol and ammonium acetate solution (3:2) adjusted with glacial acetic acid to a pH of 5.7 ± 0.2 . Add 0.1 mL of 2-mercaptoethanol per L immediately before use.

Instrument Set-Up

Figure 2 is a diagram of the HPLC/AAS interface. Components are placed inside a shop-made box of the dimensions shown. The box has a Plexiglas door at the front, and the back and top are removable. Items 1–3 are bolted to the sides of the box. Set up the remaining items as follows: Bend a 30-inch (76 cm) stainless steel tubing (item 6) as

shown to provide additional heating surface. Place the bent portion, together with the thermocouple element, between 2 disks of the heater held tightly together by a screw at the center of the upper disk. Enclose the heater assembly in 1-inch (25-mm) thick magnesia-alumina insulation, and secure to the aluminum plate support by means of the aluminum cover and screws. Push the stainless steel tubing from the heater outlet through the center of the rubber stopper (item 5) so that the end of the tubing is near the constructed portion of the condenser when the stopper is inserted tightly into the top of the condenser. Push two additional 6-inch (15-cm) lengths of the stainless steel tubing through the rubber stopper, one to serve as the nitrogen inlet and the other as the mercury vapor outlet. Connect the nitrogen inlet through the flowmeter and the mercury outlet to the test tube trap by means of spaghetti-type tubing. Connect the nitrogen tank to the flowmeter by means of spaghetti-type tubing and standard Swagelok fittings and unions. Connect the outlet from the LC column to the 0.01-inch (0.25-mm) ID stainless steel tube, which is connected to the inlet of the heating tube by standard 1/16-inch (1.6-mm) Swagelok fittings and zero dead-volume union. Connect the outlet of the test tube trap (spaghetti tubing, item 11) to the AAS cell by the small rubber stopper inserted into the side arm of the cell.

Operating Conditions for the HPLC/AAS Interface

Turning the system ON: (1) Adjust the *Mobile phase* flow rate to 0.7 mL/min. (2) Introduce water into the condenser. (3) Adjust the nitrogen sweep to 0.1 L/min (tank pressure 15 psi (1.04 kPa) and 10.0 setting on the flowmeter). (4) Gradually adjust the temperature of the interface heater to 550° (transformer setting approximately 65). (5) After the temperature reaches 550°, check the system stability by injecting several aliquots of methylmercury standard solutions. (The retention time of methylmercury is 5–6 min.)

The precision between the methylmercury peak heights should be NMT 5%. Inject all standard solutions to check linearity. If these parameters cannot be achieved, check for leaks or, after long use, replace the effluent tubing. [NOTE—To conserve analytical standard solutions, another set of standards of the same concentration may be prepared by direct dilution of *Methylmercuric chloride stock standard solution* with *Sodium thiosulfate solution*. Use these standards only for instrument checking. To prepare solutions of 0.05, 0.100, 0.150, 0.200, and 0.250 µg Hg/100 µL, dilute 100 µg Hg/mL of *Methylmercuric chloride stock standard solution* with *Sodium thiosulfate solution* as follows: 1, 1, 3, 2, and 5 mL to 200, 100, 200, 100, and 200 mL, respectively.]

Turning the system OFF: (1) Turn off the interface heater, and let the system cool to near room temperature. (2) Shut off other components, but do not shut off the *Mobile phase* flow while the heater is hot. If this is done, carbon may deposit and clog the effluent tube. For the same reason, do not pump neat organic solvents, such as methanol, to clean the column while the heater is hot. (3) After the heater has cooled to room temperature, pump methanol to rinse the column.

Preparation of Sample Solutions

For supplements in tablet form: Weigh and finely powder NLT 20 tablets. Transfer an accurately weighed portion of about 10.0 g of the powder to a 100-mL beaker. Prepare an analytical mixture by adding *Hydrochloric acid solution* so that the mass of the analytical portion of the powdered tablets plus the mass of the *Hydrochloric acid solution* totals 25.00 ± 0.30 g. Blend the analytical mixture in a homogenizer (approximately 1 min) to obtain a fine suspension. Immediately weigh 10.0 g of the fine suspension into a beaker containing 10 g of *Chromatographic siliceous earth*, and mix well. Quantitatively transfer the mixture to a glass chromatographic column containing a pledget of glass wool at the bottom. Compact the mixture moderately with a tamping rod to a height of approximately 8 cm, and place the pledget of glass wool on top. Elute the column by adding 20 mL followed by four 5-mL aliquots of chloroform. Collect the first 20 mL of the eluate in a tall 25-mL glass-stoppered graduated cylinder. Add 4.0 mL of *Sodium thiosulfate solution*, shake the mixture gently for 1 min, and allow to stand for 5 min. Transfer the upper aqueous layer containing the methylmercury–thiosulfate complex together with any emulsion into a 25-mL Erlenmeyer flask. Blow a moderately strong stream of nitrogen into the flask for 1–2 min to break up any emulsion, and expel droplets of chloroform.

[NOTE—To aid in breaking the emulsion, hold and rotate the flask at a 45-degree angle with one hand, and direct the

nitrogen stream at the thin layer of emulsion that adheres to the bottom of the flask as it rotates.

[NOTE—Some supplements may produce cloudy extracts. If this occurs, the extract can be passed through a membrane filter.]

For supplements in capsule form: Weigh accurately NLT 20 capsules and determine the average weight. Place a number of capsules equivalent to about 10.0 g in a 100-mL beaker, and add the *Hydrochloric acid solution* so that the mass of the analytical portion of capsules taken plus the mass of the *Hydrochloric acid solution* totals 25.00 ± 0.30 g. Proceed as directed in *For Supplements in Tablet Form* beginning with “Blend the analytical mixture...”.

For supplements in liquid form: Weigh accurately 10.0 g of the liquid in a 100-mL beaker, and prepare an analytical mixture by adding *Hydrochloric acid solution* so that the mass of the analytical portion of the dietary supplement liquid taken plus the mass of the *Hydrochloric acid solution* totals 25.00 ± 0.30 g. Proceed as directed in *For Supplements in Tablet Form* beginning with “Blend the analytical mixture...”.

Preparation of the Reagent Blank Solution

Prepare the reagent blank analytical solution by weighing 25.00 g of *Hydrochloric acid solution* into a 100-mL beaker. Proceed as directed in *Preparation of Sample Solutions, For Supplements in Tablet Form*, beginning with “Immediately weigh 10.0 g...”.

Preparation of Standard Solutions

Prepare 0.050, 0.100, 0.150, 0.200, and 0.250 µg Hg/100 µL of *Standard solutions* by adding, respectively, 20-, 40-, 60-, 80-, and 100-µL aliquots of *Methylmercuric chloride stock standard solution* to 20 mL of chloroform in separate 25-mL glass-stoppered graduated cylinders. Proceed as directed in *Preparation of Sample Solutions, For Supplements in Tablet Form*, beginning with “Add 4.0 mL of *Sodium thiosulfate solution*...”.

Chromatographic System

(See *Chromatography* (621).)

Mode: LC

Detector: Cold vapor atomic absorption at 253.7 nm

Guard column: 2.1-mm × 7-cm; packing L2

Analytical column: 4.6-mm × 25-cm; packing L1

Injection volume: 100 µL

Analysis

Inject the *Sample solution* into the HPLC/AAS system. After the methylmercury peak appears, inject a 100-µL aliquot of *Standard solution* that produces a peak height equal to or slightly higher than the *Sample solution* peak height. Repeat by injecting the *Sample solution* again, followed by the selected *Standard solution*. If the *Sample solution* peak height is higher than the peak height for the highest standard, dilute quantitatively an appropriate aliquot of *Sample solution* with *Sodium thiosulfate solution*. Account for the dilution in the final calculation.

Calculations

Additional dilutions must be accounted for in the final calculation. Do not vary the injection volume.

Measure peak heights above the base line, and calculate the methyl-bound mercury concentration in the test portion, in $\mu\text{g Hg/g}$, by comparing the average peak heights of the *Sample solution* to the average peak heights of the *Standard solution* as follows:

$$\text{Result } (\mu\text{g/g}) = (r_T/r_S) \times (W_S/W_T)$$

r_T = average peak height of the *Sample solution* (A)

r_S = average peak height of the *Standard solution* (A)

W_S = amount of standard injected ($\mu\text{g Hg}$)

W_T = amount of analytical portion injected (g)

where

$$W_T = (D/E) \times [F \times (0.100 \text{ mL}/4.0 \text{ mL})]$$

D = weight of the analytical portion (g)

E = weight of the analytical mixture prepared (g)

F = weight of the analytical mixture added to the *Chromatographic siliceous earth* (g)

If necessary, correct the peak height for the *Sample solution* using the response of the diluted *Reagent blank solution*.

The quantitation limit, defined as 10 times the standard deviation of the reagent blank, is $0.006 \mu\text{g Hg}/100 \mu\text{L}$ injected. This corresponds to a quantitation limit of $0.06 \mu\text{g Hg/g}$ for a 10-g analytical portion treated according to the procedure. The intraday variation, calculated as the standard deviation of five replicate injections of duplicate sample preparations, is NMT 0.12 and the relative standard deviation is NMT 20%. ■1S (USP36)

Reagents, Indicators and Solutions

This section deals with the reagents and solutions required in conducting the Pharmacopeial and the National Formulary tests and assays.

As is stated in the *General Notices*, listing of reagents, indicators, and solutions in the Pharmacopeia in no way implies that they have therapeutic utility; thus, any reference to the USP in their labeling is to include the term “reagent” or “reagent grade.”

Reagents required in the tests and assays for the Pharmacopeial and National Formulary articles are listed in this section, generally with specifications appropriate to their intended uses. Exceptions to the latter include those reagents for which corresponding specifications are presented in the current edition of *Reagent Chemicals*, published by the American Chemical Society, and reagents for which specifications could not be drafted in time for inclusion here. Thus, where it is directed to “Use ACS reagent grade,” it is intended that a grade meeting the corresponding specifications of the current edition of *ACS Reagent Chemicals* shall be used. Where no such specifications exist, and where it is directed to “Use a suitable grade,” the intent is that a suitable reagent grade available commercially shall be used. Occasionally, additional test(s) augment the designation “suitable grade,” as indicated in the text. Listed also are some, but not all, reagents that are required only in determining the quality of other reagents. For those reagents that are not listed, satisfactory specifications are available in standard reference works.

In those instances in which a reagent required in a Pharmacopeial or National Formulary test or assay need not be of analytical reagent quality, it suffices to refer to the monograph for that article appearing in this Pharmacopeia or the National Formulary or the current edition of the Food Chemicals Codex (FCC). In such cases it is to be understood that the specifications are minimum requirements and that any substance meeting more rigid specifications for chemical purity is suitable.

Where the name of a reagent specified in a test or assay is the same as the title of a USP or NF article, and it does not appear among the following *Reagent Specifications*, a substance meeting the requirements of the USP or NF monograph is to be used (e.g., *Benzocaine*, USP; or *Propylparaben*, NF). However, reference is specifically made, under *Reagent Specifications*, to a reagent bearing the name of a USP or NF article: (1) where there are requirements for a reagent in addition to the USP or NF monograph requirements (e.g., *Sodium Salicylate*, USP; or *Isopropyl Myristate*, NF), (2) where a source other than the USP or NF monograph is specified (e.g., *Lactose*, ACS reagent; or *Hydrochloric Acid*, ACS reagent), (3) where complete reagent specifications differ from the USP or NF monograph standards (e.g., *Calcium Lactate*; or *Thymol*), or (4) where a standard material is included among the reagent specifications (e.g., *Calcium Carbonate*, primary standard; or *Sodium Carbonate*, primary standard).

Reagents and solutions should be preserved in tight containers made of resistant glass or other suitable material. Directions for storage in light-resistant containers should be carefully observed.

Stoppers and stopcocks brought into contact with substances capable of attacking or penetrating their surfaces may be given a protective coating of a thin film of a suitable lubricant unless specifically interdicted.

Where a particular brand or source of a material or piece of equipment, or the name and address of a manufacturer, is mentioned, this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification.

Atomic absorption and flame photometry require the use of a number of metal-ion standard solutions. While the individual monographs usually provide directions for preparation of these solutions, use of commercially prepared standardized solutions of the appropriate ions is permissible, provided that the analyst confirms the suitability of the solutions and has data to support their use.

Reagents are substances used either as such or as constituents of solutions.

Indicators are reagents used to determine the specified endpoint in a chemical reaction, to measure hydrogen-ion concentration (pH), or to indicate that a desired change in pH has been effected. They are listed together with indicator test papers.

Buffer Solutions are referred to separately.

Colorimetric Solutions, abbreviated “CS,” are solutions used in the preparation of colorimetric standards for comparison purposes.

Test Solutions, abbreviated “TS,” are solutions of reagents in such solvents and of such definite concentrations as to be suitable for the specified purposes.

Volumetric Solutions, abbreviated “VS” and known also as **Standard Solutions**, are solutions of reagents of known concentration intended primarily for use in quantitative determinations. Concentrations are usually expressed in terms of normality.

Water—As elsewhere in the Pharmacopeia, where “water”, without qualification, is mentioned in the tests for reagents or in directions for preparing test solutions, etc., Purified Water (USP monograph) is always to be used. *Carbon dioxide-free water* is Purified Water that has been boiled vigorously for 5 minutes or more and allowed to cool while protected from absorption of carbon dioxide from the atmosphere, or Purified Water that has a resistivity of not less than 18 Mohm-cm. *Deaerated water*, for purposes other than dissolution and drug release testing, is Purified Water that has been treated to reduce the content of dissolved air by suitable means, such as by boiling vigorously for 5 minutes and cooling or by the application of ultrasonic vibration. *Particle-free water* is water that has been passed through a 0.22- μ m filter.

Organic-free water is Purified Water that produces no significantly interfering peaks when chromatographed as it is indicated in *Identification*, *Control*, and *Quantification of Residual Solvents* under *Residual Solvents* (467).

Chromatographic Solvents and Carrier Gases—The chromatographic procedures set forth in the Pharmacopeia may require use of solvents and gases that have been especially purified for such use. The purpose may be (a) to exclude certain impurities that interfere with the proper conduct of the test procedure, or (b) to extend the life of a column by reducing the build-up of impurities on the column. Where solvents and gases are called for in chromatographic procedures, it is the responsibility of the analyst to ensure the suitability of the solvent or gas for the specific use. Solvents and gases suitable for specific high-pressure or other chromatographic uses are available as specialty products from various reagent supply houses, although there is

no assurance that similar products from different suppliers are of equivalent suitability in any given procedure. The reagent specifications provided herein are for general analytical

uses of the solvents and gases and not for chromatographic uses for which the especially purified specialty products may be required.

Reagents

For the purposes of the following specifications, these definitions apply: A *blank* consists of the same quantities of the same reagents treated in the same manner as the specimen under test. A *control* is a blank to which has been added the limiting quantity of the substance being tested for, or is a specified comparison solution prepared as directed in the particular test.

The values given in boldface type following chemical symbols and formulas represent, respectively, atomic and molecular weights of the substances concerned.

Color and turbidity comparisons are to be made in color-comparison tubes that are matched as closely as possible in internal diameter and in all other respects, as directed for *Visual Comparison* under *Spectrophotometry and Light-scattering* (851). Such tubes frequently are called "Nessler tubes."

In making visual comparisons of the densities of turbid fluids, compensate for differences in color, if necessary, by viewing the turbidity through a column of water, the depth of which is determined by the volume specified in the individual reagent specification. Place the water in color-comparison tubes, and hold one of the tubes above the control tube and the other below the specimen tube.

Where an expression such as "Retain the filtrate" appears it is to be understood, unless otherwise indicated, that the washings of the residue are not to be added to the filtrate obtained. In the test heading, *Calcium, magnesium, and R₂O₃ precipitate*, the expression *R₂O₃* is intended to indicate the residue on ignition from compounds precipitated upon the addition of ammonium hydroxide, such as Fe₂O₃ and Al₂O₃.

GENERAL TESTS FOR REAGENTS

The following general test methods are provided for the examination of reagents to determine their compliance with the specifications of the individual reagents and are to be used unless it is otherwise directed in such specifications.

Boiling or Distilling Range for Reagents

Use the following procedure for determining the boiling or distilling range of reagents, unless otherwise directed in the individual specifications:

APPARATUS—Use apparatus similar to that specified for *Distilling Range—Method I* (721), except that the distilling flask is to be of 250-mL capacity, to have a short neck, and to be connected to the condenser by means of a three-way connecting tube fitted with standard-taper ground joints.

PROCEDURE—Place the distilling flask in an upright position in the perforation in the asbestos board, and connect it to the condenser.

Measure 100 mL of the liquid to be tested in a graduated cylinder, and transfer to the boiling flask together with some device to prevent bumping. Use the cylinder as the receiver for the distillate. Insert the thermometer, and heat so as to distill at the rate of 3 mL to 5 mL per minute. Make a preliminary trial, if necessary, to determine the adjustment for the proper rate of heating. Read the thermometer when about 20 drops have distilled and thereafter at volumes of distillate of 5, 10, 40, 50, 60, 90, and 95 mL. Continue the distillation until the dry point is reached.

The *Boiling or Distilling Range* is the interval between the temperatures when 1 mL and 95 mL, respectively, have distilled.

Arsenic in Reagents

Select reagents for this test for a low arsenic content, so that a blank test results in either no stain or one that is barely perceptible.

APPARATUS—Prepare a generator by fitting a 1-hole rubber stopper into a wide-mouth bottle of about 60-mL capacity. Through the perforation insert a vertical exit tube about 12 cm in total length and 1 cm in diameter along the entire upper portion (for about 8 cm) and constricted at its lower extremity to a tube about 4 cm in length and about 5 mm in diameter. The smaller portion of the tube should extend to just slightly below the stopper. Place washed sand or a pledget of purified cotton in the upper portion to about 3 cm from the top of the tube. Moisten the sand or cotton uniformly with lead acetate TS, and remove any excess or adhering droplets of the latter from the walls of the tube. Into the upper end of this tube fit a second glass tube 12 cm in length, having an internal diameter of 2.5 to 3 mm, by means of a rubber stopper. Just before running the test, place a strip of mercuric bromide test paper (see under *Indicator and Test Papers*) in this tube, crimping the upper end of the strip so that it will remain in position about 2 cm above the rubber stopper. Clean and dry the tube thoroughly each time it is used.

STANDARD ARSENIC SOLUTION—Use *Standard Preparation* prepared as directed under *Arsenic* (211).

TEST PREPARATION—Add 1 mL of sulfuric acid to 5 mL of a solution of the chemical substance (1 in 25), unless another quantity is directed in the individual reagent specification. Omit its addition entirely in the case of inorganic acids. Unless especially directed otherwise, add 10 mL of sulfurous acid. Evaporate the liquid in a small beaker, on a steam bath, until it is free from sulfurous acid and has been reduced to about 2 mL in volume. Dilute with water to 5 mL to obtain the *Test Preparation*. Substances subjected to special treatments specified in the individual reagent specification may be used directly as the *Test Preparation*.

[NOTE—Solutions prepared by the dissolving of the chemical substances in dilute acids are not considered to have undergone special treatment.]

STANDARD STAIN—Place in the generator bottle 5 mL of potassium iodide TS, 2.0 mL of *Standard Arsenic Solution*, 5 mL of acid stannous chloride TS, and 28 mL of water. Add 1.5 g of granulated zinc (in No. 20 powder), and immediately insert the stopper containing the exit tube. Keep the generator bottle immersed in water at 25° during the period of the test to moderate the reaction so that the stain will take the form of a distinctive band to facilitate the comparison of color intensity. When evolution of hydrogen has continued for 1 hour, remove the mercuric bromide test paper for comparison. This stain represents 2 µg of arsenic.

PROCEDURE—Pipet into the generator bottle 5 mL of potassium iodide TS and 5 mL of the *Test Preparation*, and add 5 mL of acid stannous chloride TS. Set the apparatus aside at room temperature for a period of 10 minutes, then add 25 mL of water and 1.5 g of granulated zinc (in No. 20 powder), and proceed as directed under *Standard Stain*. Remove the mercuric bromide test paper, and compare the stain upon it with the *Standard Stain*: the stain produced by the chemical tested does not exceed the standard stain in length or in intensity of color, indicating not more than 10 parts of arsenic per million parts of the substance being tested. Since light, heat, and moisture cause the stain to

fade rapidly, place the papers in clean, dry tubes, and make comparisons promptly.

INTERFERING CHEMICALS—*Antimony*, if present in the substance being tested, produces a gray stain. *Sulfites*, *sulfides*, *thiosulfates*, and other compounds that liberate hydrogen sulfide or sulfur dioxide when treated with sulfuric acid must be oxidized by means of nitric acid and then reduced by means of sulfur dioxide as directed under *Test Preparation* before they are placed in the apparatus. Certain *sulfur compounds*, as well as *phosphine*, give a bright yellow band on the test paper. If *sulfur compounds* are present, the lead acetate-moistened cotton or sand will darken. In that case, repeat the operation as directed under *Test Preparation* upon a fresh portion of the solution being tested and use greater care in effecting the complete removal of the sulfurous acid. In testing hypophosphites, observe special care to oxidize completely the solution being tested as directed, otherwise the evolution of phosphine may result in a yellow stain which may be confused with the orange-yellow color produced by arsine. The stain produced by phosphine may be differentiated from that given by arsine by means of moistening it with 6 N ammonium hydroxide. A stain caused by arsine becomes dark when so treated, but a stain produced by phosphine does not materially change in color.

Chloride in Reagents

STANDARD CHLORIDE SOLUTION—Dissolve 165.0 mg of dried sodium chloride in water to make 1000.0 mL. This solution contains the equivalent of 0.10 mg of chlorine (Cl) in each mL.

PROCEDURE—Neutralize, if alkaline, a solution of the quantity of the reagent indicated in the test in 25 mL of water, or a solution prepared as directed in the test, with nitric acid, litmus paper being used as the indicator, and add 3 mL more of nitric acid. Filter the solution, if necessary, through a filter paper previously washed with water until the paper is free from chloride, and add 1 mL of silver nitrate TS. Mix, and allow to stand for 5 minutes protected from direct sunlight. Compare the turbidity, if any, with that produced in a control made with the same quantities of the same reagents as in the final test and a volume of *Standard Chloride Solution* equivalent to the quantity of chloride (Cl) permitted by the test. Adjust the two solutions with water to the same volume before adding the silver nitrate TS, and compare the turbidities.

In *testing barium salts*, neutralize, if alkaline, the solution containing the reagent, with nitric acid, and add only 3 drops more of nitric acid. Conduct the remainder of the test as described previously.

In *testing salts giving colored solutions*, dissolve 2 g of the reagent in 25 mL of water, and add 3 mL of nitric acid. Filter the solution, if necessary, through a filter paper previously washed with water, and divide the filtrate into two equal portions. Treat one portion with 1 mL of silver nitrate TS, allow to stand for 10 minutes, and, if any turbidity is produced, filter it through a washed filter paper until clear, and use the filtrate as a blank. Treat the other portion with 1 mL of silver nitrate TS, mix, and allow to stand for 5 minutes protected from direct sunlight. Compare the turbidity with that produced in the blank by the addition of a volume of *Standard Chloride Solution* equivalent to the quantity of chloride (Cl) permitted in the test, both solutions being adjusted with water to the same volume.

Flame Photometry for Reagents

The use of flame photometric procedures to determine traces of calcium, potassium, sodium, and strontium is called for in some of the reagent specifications. The suitability of such determinations depends upon the use of adequate apparatus, and several instruments of suitable selectiv-

ity are available. The preferred type of flame photometer is one that has a red-sensitive phototube, a multiplier phototube, a monochromator, an adjustable slit-width control, a selector switch, and a sensitivity control. Other types of photometers may be used, provided the operator has proved that the instrument will determine accurately the amount of impurities permitted in the reagent to be tested.

The flame photometric procedures depend upon the use of semi-internal standards, and thus require both a *Sample Solution* and a *Control Solution*. For the *Sample Solution*, a specified weight of specimen is dissolved and diluted to a definite volume. For the *Control Solution*, the same amount of specimen is dissolved, the limiting amounts of the suspected impurities are added, and the solution is then diluted to the same definite volume as the *Sample Solution*. The flame photometer is set as directed in the general procedures and then adjusted to give an emission reading as near 100% transmittance as is possible with the *Control Solution* at the wavelength specified for the particular impurity concerned. With the instrument settings left unchanged, the emission from the *Sample Solution* is read at the same wavelength and at a specified background wavelength. The background reading is then used to correct the observed emission of the *Sample Solution* for the emission due to the specimen and the solvent. The specimen being tested contains less than the specified limit of impurity if the difference between the observed background and total emissions for the *Sample Solution* is less than the difference between the observed emissions for the *Control Solution* and the *Sample Solution* at the wavelength designated for the particular impurity.

CALCIUM IN REAGENTS—

Standard Calcium Solution—Dissolve 250 mg of calcium carbonate in a mixture of 20 mL of water and 5 mL of diluted hydrochloric acid, and when solution is complete, dilute with water to 1 L. This solution contains 0.10 mg of calcium (Ca) per mL.

Procedure—Use the *Sample Solution* and the *Control Solution* prepared as directed in the individual test procedure.

Set the slit-width control of a suitable flame photometer at 0.03 mm, and set the selector switch at 0.1. Adjust the instrument to give the maximum emission with the *Control Solution* at the 422.7-nm calcium line, and record the transmittance. Without changing any of the instrument settings, record the transmittance for the emission of the *Sample Solution* at 422.7 nm. Change the monochromator to the wavelength specified in the individual test procedure, and record the background transmittance for the background emission of the *Sample Solution*: the difference between the transmittances for the *Sample Solution* at 422.7 nm and at the background wavelength is not greater than the difference between transmittances observed at 422.7 nm for the *Sample Solution* and the *Control Solution*.

POTASSIUM IN REAGENTS—

Standard Potassium Solution—Dissolve 191 mg of potassium chloride in a few mL of water, and dilute with water to 1 L. Dilute a portion of this solution with water in the ratio of 1 to 10 to obtain a concentration of 0.01 mg of potassium (K) per mL.

Procedure—Use the *Sample Solution* and the *Control Solution* prepared as directed in the individual test procedure.

[NOTE—In testing calcium salts, use an oxyhydrogen burner.]

Set the slit-width control of a suitable flame photometer equipped with a red-sensitive detector at 0.1 mm, unless otherwise directed, and set the selector switch at 0.1. Adjust the instrument to give the maximum emission with the *Control Solution* at the 766.5-nm potassium line, and record the transmittance. Without changing any of the instrument settings, record the transmittance for the emission of the *Sample Solution* at 766.5 nm. Change the monochromator to 750 nm, and record the background transmittance for the background emission of the *Sample Solution*: the difference

between the transmittances for the *Sample Solution* at 766.5 nm and 750 nm is not greater than the difference between transmittances observed at 766.5 nm for the *Sample Solution* and the *Control Solution*.

SODIUM IN REAGENTS—

Standard Sodium Solution—Dissolve 254 mg of sodium chloride in a few mL of water, and dilute with water to 1 L. Dilute a portion of this solution with water in the ratio of 1 to 10 to obtain a concentration of 0.01 mg of sodium (Na) per mL.

Procedure—Use the *Sample Solution* and the *Control Solution* prepared as directed in the individual test procedure.

Set the slit-width control of a suitable flame photometer at 0.01 mm, and set the selector switch at 0.1. Adjust the instrument to give the maximum emission with the *Control Solution* at the 589-nm sodium line, and record the transmittance. Without changing any of the instrument settings, record the transmittance for the emission of the *Sample Solution* at 589 nm. Change the monochromator to 580 nm, and record the background transmittance for the background emission of the *Sample Solution*: the difference between the transmittances for the *Sample Solution* at 589 and 580 nm is not greater than the difference between transmittances observed at 589 nm for the *Sample Solution* and the *Control Solution*.

STRONTIUM IN REAGENTS—

Standard Strontium Solution—Dissolve 242 mg of strontium nitrate in a few mL of water, and dilute with water to 1 L. Dilute a portion of this solution with water in the ratio of 1 to 10 to obtain a concentration of 0.01 mg of strontium (Sr) per mL.

Procedure—Use the *Sample Solution* and the *Control Solution* prepared as directed in the individual test procedure.

Set the slit-width control of a suitable flame photometer at 0.03 mm, and set the selector switch at 0.1. Adjust the instrument to give the maximum emission with the *Control Solution* at the 460.7-nm strontium line, and record the transmittance. Without changing any of the instrument settings, record the transmittance for the emission of the *Sample Solution* at 460.7 nm. Change the monochromator to the wavelength specified in the individual test procedure, and record the background transmittance for the background emission of the *Sample Solution*: the difference between the transmittances for the *Sample Solution* at 460.7 nm and at the background wavelength is not greater than the difference between transmittances observed at 460.7 nm for the *Sample Solution* and the *Control Solution*.

Heavy Metals in Reagents

STANDARD LEAD SOLUTION—Use *Standard Lead Solution* (see *Heavy Metals* (231)). Each mL of this solution contains the equivalent of 0.01 mg of Pb.

PROCEDURE—Unless otherwise directed, test for heavy metals as follows:

(a) If the heavy metals limit is 0.0005% (5 ppm), dissolve 6.0 g of the specimen in water to make 42 mL.

(b) If the heavy metals limit is 0.001% (10 ppm) or more, or in the event of limited solubility, use 4 g, and dissolve in water to make 40 mL, warming, if necessary, to aid solution.

For the control, transfer 7 mL of the solution from (a) to a color-comparison tube, and add a volume of *Standard Lead Solution* equivalent to the amount of lead permitted in 4 g of the reagent. Dilute with water to 35 mL, and add diluted acetic acid, or ammonia TS, until the pH is about 3.5, determined potentiometrically, then dilute with water to 40 mL, and mix. Transfer the remaining 35 mL of the solution from (a) to a color-comparison tube closely matching that used for the control, and add diluted acetic acid, or ammonia TS, until the pH is about 3.5, determined potentiometrically, then dilute with water to 40 mL, and mix. Then to each

tube add 10 mL of hydrogen sulfide TS, mix, and compare the colors by viewing through the color-comparison tube downward against a white surface. The color in the test specimen is not darker than that of the control.

If the solution of the reagent is prepared as in (b), use for the control 10 mL of the solution, and add to it a volume of *Standard Lead Solution* equivalent to the amount of lead permitted in 2 g of the reagent. Dilute the remaining 30 mL of solution (b) with water to 35 mL, and proceed as directed in the preceding paragraph, beginning with "add diluted acetic acid, or ammonia TS," in the second sentence.

If the reagent to be tested for heavy metals is a salt of an aliphatic organic acid, substitute 1 N hydrochloric acid for the diluted acetic acid specified in the foregoing method.

Insoluble Matter in Reagents

Dissolve the quantity of reagent specified in the test in 100 mL of water, heat to boiling unless otherwise directed, in a covered beaker, and warm on a steam bath for 1 hour. Filter the hot solution through a tared sintered-glass crucible of fine porosity. Wash the beaker and the filter thoroughly with hot water, dry at 105°, cool in a desiccator, and weigh.

Loss on Drying for Reagents

Determine as directed under *Loss on Drying* (731).

Nitrate in Reagents

STANDARD NITRATE SOLUTION—Dissolve 163 mg of potassium nitrate in water, add water to make 100 mL, and dilute 10 mL of this solution with water to 1 liter, to obtain a solution containing the equivalent of 0.01 mg of NO₃ per mL.

BRUCINE SULFATE SOLUTION—Dissolve 600 mg of brucine sulfate in 600 mL of nitrate-free, dilute sulfuric acid (2 in 3) that previously has been cooled to room temperature, and dilute with the acid to 1 L. [NOTE—Prepare the nitrate-free sulfuric acid by adding 4 parts of sulfuric acid to 1 part of water, heating the solution to dense fumes of sulfur trioxide, and cooling. Repeat the dilution and heating three or four times.]

SAMPLE SOLUTION—To the weight of sample specified in the individual reagent specification, dissolved in the designated volume of water, add *Brucine Sulfate Solution* to make 50 mL.

CONTROL SOLUTION—To a volume of *Standard Nitrate Solution* equivalent to the weight of nitrate (NO₃) specified in the individual reagent specification, add the weight of sample specified in the individual reagent specification and then add *Brucine Sulfate Solution* to make 50 mL.

BLANK SOLUTION—Use 50 mL of *Brucine Sulfate Solution*.

PROCEDURE—Heat the *Sample Solution*, *Control Solution*, and *Blank Solution* in a boiling water bath for 10 minutes, then cool rapidly in an ice bath to room temperature. Adjust a suitable spectrophotometer to zero absorbance at 410 nm with the *Blank Solution*. Determine the absorbance of the *Sample Solution*, note the result, and adjust the instrument to zero absorbance with the *Sample Solution*. Determine the absorbance of the *Control Solution*: the absorbance reading for the *Sample Solution* does not exceed that for the *Control Solution*.

Nitrogen Compounds in Reagents

PROCEDURE—Unless otherwise directed, test for nitrogen compounds as follows: Dissolve the specified quantity of test specimen in 60 mL of ammonia-free water in a Kjeldahl flask

connected through a spray trap to a condenser, the end of which dips below the surface of 10 mL of 0.1 N hydrochloric acid. Add 10 mL of freshly boiled sodium hydroxide solution (1 in 10) and 500 mg of aluminum wire, in small pieces, to the Kjeldahl flask, and allow to stand for 1 hour, protected from loss of, and exposure to, ammonia. Distill 35 mL, and dilute the distillate with water to 50 mL. Add 2 mL of freshly boiled sodium hydroxide solution (1 in 10), mix, add 2 mL of alkaline mercuric-potassium iodide TS, and again mix: the color produced is not darker than that of a control containing the amount of added N (as ammonium chloride) specified in the individual test procedure.

Phosphate in Reagents

STANDARD PHOSPHATE SOLUTION—Dissolve 143.3 mg of dried monobasic potassium phosphate, KH_2PO_4 , in water to make 1000.0 mL. This solution contains the equivalent of 0.10 mg of phosphate (PO_4) in each mL.

PHOSPHATE REAGENT A—Dissolve 5 g of ammonium molybdate in 1 N sulfuric acid to make 100 mL.

PHOSPHATE REAGENT B—Dissolve 200 mg of *p*-methylaminophenol sulfate in 100 mL of water, and add 20 g of sodium bisulfite. Store this reagent in well-filled, tightly stoppered bottles, and use within one month.

PROCEDURE—[NOTE—The tests with the specimen and the control are made preferably in matched color-comparison tubes.] Dissolve the quantity of the reagent specified in the test, or the residue obtained after the prescribed treatment, in 20 mL of water, by warming, if necessary, add 2.5 mL of dilute sulfuric acid (1 in 7), and dilute with water to 25 mL. (If preferable, the test specimen or the residue may be dissolved in 25 mL of approximately 0.5 N sulfuric acid.) Then add 1 mL each of *Phosphate Reagents A* and *B*, mix, and allow to stand at room temperature for 2 hours. Compare any blue color produced with that produced in a control made with the same quantities of the same reagents as in the test with the specimen, and a volume of *Standard Phosphate Solution* equivalent to the quantity of phosphate (PO_4) designated in the reagent specifications.

Residue on Ignition in Reagents

PROCEDURE—Unless otherwise directed, determine the residue on ignition as follows: Weigh accurately 1 to 2 g of the substance to be tested in a suitable crucible that previously has been ignited, cooled, and weighed. Ignite the substance, gently and slowly at first and then at a more rapid rate, until it is thoroughly charred, if organic in nature, or until it is completely volatilized, if inorganic in nature. If the use of sulfuric acid is specified, cool the crucible, add the specified amount of acid, and ignite the crucible gently until fumes no longer are evolved. Then ignite the crucible at $800 \pm 25^\circ$, cool in a suitable desiccator, and weigh. If the use of sulfuric acid is not specified, the crucible need not be cooled but can be ignited directly at $800 \pm 25^\circ$ once the charring or volatilization is complete. Continue the ignition until constant weight is attained, unless otherwise specified.

Conduct the ignition in a well-ventilated hood, but protected from air currents, and at as low a temperature as is possible to effect the complete combustion of the carbon. A muffle furnace may be used, if desired, and its use is recommended for the final ignition at $800 \pm 25^\circ$.

Sulfate in Reagents

STANDARD SULFATE SOLUTION—Dissolve 181.4 mg of potassium sulfate (dried at 105° for 2 hours) in water to make 1000 mL. This solution contains the equivalent of 0.10 mg of sulfate (SO_4) per mL.

PROCEDURE—

Method I—Neutralize, if necessary, a solution of the quantity of the reagent or residue indicated in the test in 25 mL of water, or a solution prepared as directed in the test, with hydrochloric acid or with ammonia TS, litmus paper being used as the indicator, and add 1 mL of 1 N hydrochloric acid. Filter the solution, if necessary, through a filter paper previously washed with water, and add 2 mL of barium chloride TS. Mix, allow to stand for 10 minutes, and compare the turbidity, if any, with that produced in a control containing the same quantities of the same reagents used in the test and a quantity of *Standard Sulfate Solution* equivalent to the quantity of sulfate (SO_4) permitted in the test. Adjust the two solutions with water to the same volume before adding the barium chloride TS.

Method II—Heat to boiling the solution, prepared as directed in the individual test procedure, or the filtrate designated in the procedure, and add 5 mL of barium chloride TS. Then digest the solution on a steam bath for 2 hours, and allow to stand overnight. If any precipitate is formed, filter the solution through paper, wash the residue with hot water, and transfer the paper containing the residue to a tared crucible. Char the paper, without burning, and ignite the crucible and its contents to constant weight. Perform a blank determination concurrently with the test specimen determination, and subtract the weight of residue obtained from that obtained in the test specimen determination to obtain the weight of residue attributable to the sulfate content of the specimen.

REAGENT SPECIFICATIONS

Add the following:

■ **Alizarin Complexone** (*Alizarin-3-methyliminodiacetic Acid; Alizarin Fluorine Blue*), $\text{C}_{19}\text{H}_{15}\text{NO}_8$ —**385.32** [3952-78-1]—Use a suitable grade. ■ **TS** (USP36)

Change to read:

4-Amino-3-hydroxy-1-naphthalenesulfonic Acid
■ (*1,2,4-Aminonaphtholsulfonic Acid; 1-Amino-2-naphthol-4-sulfonic Acid*), ■ **TS** (USP36)
 $\text{C}_{10}\text{H}_9\text{NO}_4\text{S}$ —**239.25** [116-63-2]—Light purple powder. Use ACS reagent grade.

Delete the following:

■ **8-Amino-6-methoxyquinoline** (*6-Methoxy-8-aminoquinoline*), $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$ —**174.2** [90-52-8]—Use a suitable grade with a content of not less than 98.0%.
[NOTE—A suitable grade is available from www.3bmedicals.com, catalog number 3B3-002598.] ■ **TS** (USP36)

Change to read:

1,2,4-Aminonaphtholsulfonic Acid—■ See *4-Amino-3-hydroxy-1-naphthalenesulfonic Acid*. ■ **TS** (USP36)

Change to read:

Bacterial Alkaline Protease Preparation—Use a suitable grade.

[NOTE—A suitable grade is commercially available as “Protex 6L” from Genencor, www.genencor.com.] ■ **TS** (USP36)

Change to read:

Diatomaceous Earth, Flux-Calcined [91053-39-3]—Use a suitable grade.

[NOTE—A suitable grade is “Chromosorb W, AW-DMCS”. ■1S (USP36)]

Add the following:

■1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p'*-DDD), $C_{14}H_{10}Cl_4$ —**320.03** [72-54-8]—Use a suitable grade. [NOTE—A suitable grade is available as catalog number B0132 at www.tciamerica.com.] ■1S (USP36)

Change to read:

Ether, Peroxide-Free (Diethyl Ether; Ether), $(C_2H_5)_2O$ —**74.12**—Use ACS reagent grade.

Peroxide—Transfer 8 mL of potassium iodide and starch TS to a 12-mL ground glass-stoppered cylinder about 15 mm in diameter. Fill completely with the substance under test, mix, and allow to stand protected from light for 5 minutes. No color develops. Alternatively, peroxide test strips may be used.

[NOTE—Suitable peroxide test strips can be obtained from EMD Chemicals, www.emdchemicals.com.] ■1S (USP36)]

Change to read:

Lanthanum Alizarin Complexan Mixture—■Dissolve 47.9 mg of alizarin complexone in a mixture of 0.1 mL of ammonium hydroxide, 1.0 mL of 20% (w/v) ammonium acetate, and a few mL of water. Filter the solution into a 200-mL volumetric flask containing 8.2 g of anhydrous sodium acetate, 6.0 mL of glacial acetic acid, and enough water to dissolve the solids. Wash the filter with a small volume of water. Slowly add 100 mL of acetone while swirling. Dissolve 140.45 mg of lanthanum nitrate hexahydrate in 2.5 mL of 2 M hydrochloric acid, warming gently to aid dissolution. Transfer this solution to the 200-mL volumetric flask containing the aqueous acetone solution. Dilute with water to volume. Mix well, and readjust the volume after 30 min. This reagent is stable for one week. ■1S (USP36)

Add the following:

■**Methyl Hexanoate (Caproic Acid Methyl Ester; Methyl Caproate)**, $C_7H_{14}O_2$ —**130.18** [106-70-7]—Use a suitable grade with a content of NLT 99%.

[NOTE—A suitable grade is available as catalog 259942 from www.sigma-aldrich.com.] ■1S (USP36)

Add the following:

■**Methyl Palmitoleate (Methyl *cis*-9-Hexadecenoate; Palmitoleic Acid Methyl Ester)**, $C_{17}H_{32}O_2$ —**268.43** [1120-25-8]—Use a suitable grade with a content of NLT 99%. [NOTE—A suitable grade is available as catalog number P9667 or 76176 from www.sigma-aldrich.com.] ■1S (USP36)

Change to read:

Pectate Lyase [9015-75-2]—An enzyme obtained from *Aspergillus* sp. Light brown, viscous liquid. Specific gravity is about 1.5. It is readily soluble in water. It is supplied at approximately 14 units per mL at pH 8.0 in Tris-HCl buffer [50 mM of Tris(hydroxymethyl)aminomethane containing 1 mM of $CaCl_2$, pH 8.0] in a solution of 50% glycerol and 0.02% sodium azide. One unit is defined as the enzyme

activity that produces 1 μ mol of unsaturated product per minute.

Activity—

PECTIN SOLUTION—Transfer a quantity of Pectin, equivalent to 0.05 g on the dried basis, to a 100-mL volumetric flask. [NOTE—Pectin has a molecular weight of 103,000 Da; its degree of esterification (percentage of galacturonic acid groups substituted with methyl) is 12.] Moisten with 0.1 mL of 2-propanol. Add 50 mL of water to the flask, and mix the solution with a magnetic stirrer. Use 0.5 N sodium hydroxide to adjust the solution to a pH of 12. Stop the stirrer, and allow the solution to stand undisturbed at room temperature for 15 minutes. Adjust the solution with 0.5 N hydrochloric acid to a pH of 8.0. Dilute with water to volume.

TRIS BUFFER SOLUTION—Transfer 6.055 g of Tris(hydroxymethyl)aminomethane and 0.147 g of calcium chloride ■1S (USP36) to a 1000-mL volumetric flask containing 950 mL of water, and mix. Adjust the solution with 1 N hydrochloric acid to a pH of 8.0. Dilute with water to volume.

DILUTED PECTATE LYASE—Transfer 0.5 mL of Pectate Lyase to a 50-mL volumetric flask, dilute with *Tris buffer solution* to volume, and mix.

PROCEDURE—Add the solutions set forth in the table below to quartz cuvettes.

Label	Tris Buffer Solution (mL)	Pectin Solution (mL)	Diluted Pectate Lyase (mL)	Water (mL)
Enzyme blank	0.5	1.0	0	1.0
Test blank	0.5	0	0.5	1.5
Test solution	0.5	1.0	0.5	0.5

Perform the test on the solutions so obtained, using a suitable UV-Vis spectrophotometer (see *Spectrophotometry and Light-Scattering* (851)) and using water as the blank. Mix the solutions well at time 0, and immediately measure the absorbances at 235 nm. Record the value for the *Enzyme blank*, A_{0-EB} ; for the *Test blank*, A_{0-TB} ; and for the *Test solution*, A_{0-TS} . After incubation at room temperature for 30 minutes, determine the absorbance again at 235 nm for the *Enzyme blank*, A_{30-EB} ; for the *Test blank*, A_{30-TB} ; and for the *Test solution*, A_{30-TS} . One unit is defined as the enzymatic activity that produces 1 μ mol of unsaturated product from pectin per minute. Calculate the Pectate Lyase activity, in units per mL, using the following formula:

$$50(10^3)[(A_{30-TS} - A_{30-EB} - A_{30-TB}) - (A_{0-TS} - A_{0-EB} - A_{0-TB})]/30\varepsilon_{235}L$$

in which 50 is the volume, in mL, of *Diluted pectate lyase*; 10^3 is the unit conversion factor; 30 is the time, in minutes, of the reaction; ε_{235} is the molar extinction coefficient, in $M^{-1}cm^{-1}$, of the reaction product ($4600 M^{-1}cm^{-1}$); and L is the path length, in cm, of the reaction cuvette (1 cm). Alternatively, these solutions, after being mixed in the cuvettes, can be immediately measured at 235 nm continuously in a recording UV-Vis spectrophotometer set up for kinetic assays. The result is obtained by correcting the blank determination, using the *Enzyme blank* and the *Test blank*.

Change to read:

Peptone, Dried (Meat Peptone)—Reddish-yellow to brown powder, having a characteristic, but not putrescent, odor. Soluble in water, forming a yellowish-brown solution having a slight acid reaction; insoluble in alcohol and in ether.

Nitrogen ■compounds ■1S (USP36) (Reagent test)—Determine by the Kjeldahl method, using a test specimen previously dried at 105° to constant weight: between 12% and 18% of nitrogen is found.

Residue on ignition (Reagent test)—Ignite 500 mg with 1 mL of sulfuric acid: the residue weighs NMT 75 mg (15.0%).

Loss on drying (731)—Dry it at 105° to constant weight: it loses NMT 7.0% of its weight.

Coagulable protein—Heat a filtered solution (1 in 20) to boiling: no precipitate forms.

Microbial content—NMT 10⁴ cfu/g

Change to read:

Phosphomolybdic Acid, approximately 20MoO₃ · P₂O₅ · 51H₂O—3939.49 ■[51429-74-4]■^{1S} (USP36)—Use ACS reagent grade.

Add the following:

■**Polyoxyethylene 10 Lauryl Ether** (*Decaethylene Glycol Monododecyl Ether*), C₃₂H₆₆O₁₁—626.86 [6540-99-4]—Use a suitable grade. [NOTE—A suitable grade is available as catalog number P9769 at <http://www.sigma.com>.]■^{1S} (USP36)

Add the following:

■**Salicylic Acid**—Use *Salicylic Acid* (USP monograph). ■^{1S} (USP36)

Change to read:

Silica Gel, Octadecylsilanized Chromatographic—Use a suitable grade.

[NOTE—A suitable grade is available commercially as ■“Analtech Reversed Phase Uniplates” from www.spectrumchemical.com.]■^{1S} (USP36)]

Change to read:

Sodium Bitartrate, NaHC₄H₄O₆ · H₂O—190.08 ■[6131-98-2]■^{1S} (USP36)—White crystals or a crystalline powder. Soluble in cold water.

Assay—Dissolve about 500 mg, accurately weighed, in 30 mL of water, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS: each mL of 0.1 N sodium hydroxide is equivalent to 19.01 mg of NaHC₄H₄O₆ · H₂O. Between 99% and 100.5% is found.

Insoluble matter (Reagent test): not more than 1 mg, from 10 g (0.01%).

Chloride (Reagent test)—One g shows not more than 0.2 mg of Cl (0.02%).

Heavy metals (Reagent test)—Dissolve 4 g in 25 mL of water, add 2 drops of phenolphthalein TS, and then add ammonia TS, dropwise, until the solution is slightly pink. Add 4 mL of 1 N hydrochloric acid, dilute with water to 40 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing 0.04 mg of added Pb (0.001%).

Sulfate (Reagent test, *Method I*)—One g shows not more than 0.2 mg of SO₄ (0.02%).

Change to read:

Vinylpyrrolidinone (*1-Vinyl-2-pyrrolidinone*; *1-Vinyl-2-pyrrolidone*; *N-Vinylpyrrolidinone*; *N-Vinylpyrrolidone*), C₆H₉NO—111.14 ■[88-12-0]■^{1S} (USP36)—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* (621)) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-μm layer of G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 100° and programmed to rise 10° per min to 250°. The area of the C₆H₉NO peak is not less than 99.0% of the total peak area.

Water, Method 1 (921): not more than 0.1%, determined on 2.5 g, using a mixture of 50 mL of methanol and 10 mL of butyrolactone as the solvent.

[NOTE—A suitable grade is available from Merck KGaA/EMD chemicals, catalogue number 8.08518.0250, www.emdchemicals.com.]

Solutions

TEST SOLUTIONS (TS)

Certain of the following test solutions are intended for use as acid-base indicators in volumetric analyses. Such solutions should be so adjusted that when 0.15 mL of the indicator solution is added to 25 mL of carbon dioxide-free water, 0.25 mL of 0.02 N acid or alkali, respectively, will produce the characteristic color change. Similar solutions are intended for use in pH measurement. Where no special directions for their preparation are given, the same solution is suitable for both purposes.

Where it is directed that a volumetric solution be used as the test solution, standardization of the solution used as TS is not required.

In general, the directive to prepare a solution “fresh” indicates that the solution is of limited stability and must be prepared on the day of use.

For the preparation of Test Solutions, use reagents of the quality described under *Reagents*.

Change to read:

Glucose Oxidase–Chromogen TS—A solution containing, in each mL, 0.5 μmol of 4-aminoantipyrine, 22.0 μmol of sodium *p*-hydroxybenzoate, not less than 7.0 units of glucose oxidase, and not less than 0.5 units of peroxidase, and buffered to a pH of 7.0 ± 0.1.

Suitability—When used for determining glucose in Inulin, ascertain that no significant color results by reaction with fructose, and that a suitable absorbance-versus-concentration slope is obtained with glucose.

[NOTE—■Glucose oxidase can be from *Aspergillus niger*. ■^{1S} (USP36)]

Change to read:

Orthophenanthroline TS—Dissolve 150 mg of orthophenanthroline in 10 mL of a solution of ferrous sulfate, prepared by dissolving 700 mg ■^{1S} (USP36) of ferrous sulfate in 100 mL of water. The ferrous sulfate solution must be prepared immediately before dissolving the orthophenanthroline. Store in well-closed containers.

Chromatographic Columns

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE—Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

Packings

Change to read:

L21—A rigid, spherical styrene-divinylbenzene copolymer 3 to 30 μm . USP36

Change to read:

L45—Beta cyclodextrin, *R,S*-hydroxypropyl ether derivative, USP36 bonded to porous silica particles, 5 to 10 μm in diameter.

Change to read:

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, 5 USP36 to 15 μm in diameter.

Change to read:

L66—A crown ether coated on a 5- μm particle size silica gel substrate. The active site is (S)-18-crown-6-ether. [NOTE—Available as Crownpak CR(+) from www.chiraltech.com.] USP36

Supports

[NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.]

Add the following:

S1D—A support prepared from crushed firebrick and calcinated or burned with a clay binder above 900°, not acid washed. It may be silanized. USP36

Reference Tables

CONTAINERS FOR DISPENSING CAPSULES AND TABLETS

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and Storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	Container Specification
Abacavir Tablets	W
Acebutolol Hydrochloride Capsules	T
Acepromazine Maleate Tablets	T, LR
Acetaminophen Capsules	T
Acetaminophen Tablets, Extended-Release	T
Acetaminophen Tablets	T
Acetaminophen and Aspirin Tablets	T
Acetaminophen, Aspirin, and Caffeine Tablets	T
Acetaminophen and Caffeine Tablets	T
Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine, Capsules Containing at Least Three of the Following—	T
Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine, Tablets Containing at Least Three of the Following—	T
Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, Capsules Containing at Least Three of the Following—	T
Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, Tablets Containing at Least Three of the Following—	T
Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets	T
Acetaminophen and Codeine Phosphate Capsules	T, LR
Acetaminophen and Codeine Phosphate Tablets	T, LR
Acetaminophen and Diphenhydramine Citrate Tablets	T
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets	T
Acetaminophen and Pseudoephedrine Hydrochloride Tablets	T
Acetaminophen and Tramadol Hydrochloride Tablets	T
Acetazolamide Tablets	T
Acetohexamide Tablets	W
Acetohydroxamic Acid Tablets	T
Acitretin Capsules	W, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Acyclovir Capsules	T
Acyclovir Tablets	T
Albendazole Tablets	T
Albuterol Tablets	T, LR
Alendronate Sodium Tablets	T
Add the following:	
▲Alfuzosin Hydrochloride Tablets, Extended-Release	LR▲ <i>USP36</i>
Allopurinol Tablets	W
Alprazolam Tablets	T, LR
Alprazolam Tablets, Extended-Release	T, LR
Alprazolam Tablets, Orally Disintegrating	T
Altretamine Capsules	T, LR
Alumina and Magnesia Tablets	W
Alumina, Magnesia, and Calcium Carbonate Tablets	W
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets	W
Alumina, Magnesia, and Simethicone Tablets	W
Alumina and Magnesium Carbonate Tablets	T
Alumina, Magnesium Carbonate, and Magnesium Oxide Tablets	T
Alumina and Magnesium Trisilicate Tablets	W
Aluminum Carbonate Gel, Dried Basic, Capsules	W
Aluminum Carbonate Gel, Dried Basic, Tablets	W
Aluminum Hydroxide Gel, Dried, Capsules	W
Aluminum Hydroxide Gel, Dried, Tablets	W
Amantadine Hydrochloride Capsules	T
Amiloride Hydrochloride Tablets	W
Amiloride Hydrochloride and Hydrochlorothiazide Tablets	W
Aminobenzoate Potassium Capsules	W
Aminobenzoate Potassium Tablets	W
Aminocaproic Acid Tablets	T
Aminogluthethimide Tablets	T, LR
Aminopentamide Sulfate Tablets	W
Aminophylline Tablets	T
Aminophylline Tablets, Delayed-Release	T
Aminosalicylate Sodium Tablets	T, LR
Aminosalicylic Acid Tablets	T, LR
Amitriptyline Hydrochloride Tablets	W
Add the following:	
■Amlodipine and Benazepril Hydrochloride Capsules	W■ <i>US (USP36)</i>
Amlodipine Besylate Tablets	T, LR
Ammonium Chloride Tablets, Delayed-Release	T
Amodiaquine Hydrochloride Tablets	T
Amoxapine Tablets	W
Amoxicillin Capsules	T
Amoxicillin Tablets	T
Amoxicillin and Clavulanate Potassium Tablets	T

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Add the following:	
Amoxicillin and Clavulanic Acid Tablets, Extended-Release	T, LR (USP36)
Amphetamine Sulfate Tablets	W
Ampicillin Capsules	T
Ampicillin Tablets	T
Anagrelide Capsules	T, LR
Anileridine Hydrochloride Tablets	T, LR
Apomorphine Hydrochloride Tablets	T, LR
Arginine Capsules	T, LR
Arginine Tablets	T, LR
Ascorbic Acid Tablets	T, LR
Aspirin Capsules	T
Aspirin Capsules, Delayed-Release	T
Aspirin Tablets	T
Aspirin Tablets, Buffered	T
Aspirin Tablets, Delayed-Release	T
Aspirin Tablets, Effervescent for Oral Solution	T
Aspirin Tablets, Extended-Release	T
Aspirin, Alumina, and Magnesia Tablets	T
Aspirin, Alumina, and Magnesium Oxide Tablets	T
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules	T
Aspirin and Codeine Phosphate Tablets	W, LR
Aspirin, Codeine Phosphate, Alumina, and Magnesia Tablets	W, LR
Astemizole Tablets	T
Atenolol Tablets	W
Atenolol and Chlorthalidone Tablets	W
Atropine Sulfate Tablets	W
Azatadine Maleate Tablets	W
Azathioprine Tablets	LR
Azithromycin Capsules	W
Azithromycin Tablets	T
Bacampicillin Hydrochloride Tablets	T
Baclofen Tablets	W
Balsalazide Disodium Capsules	T
Barium Sulfate Tablets	W
Belladonna Extract Tablets	T, LR
Benazepril Hydrochloride Tablets	W
Bendroflumethiazide Tablets	T
Benzonate Capsules	T, LR
Benztropine Mesylate Tablets	W
Beta Carotene Capsules	T, LR
Betamethasone Tablets	T
Betaxolol Tablets	T
Bethanechol Chloride Tablets	T
Bicalutamide Tablets	T
Biperiden Hydrochloride Tablets	T
Bisacodyl Tablets	T
Bisacodyl Tablets, Delayed-Release	W
Bismuth Subsalicylate Tablets	T
Bisoprolol Fumarate Tablets	T, LR
Bisoprolol Fumarate and Hydrochlorothiazide Tablets	W
Black Cohosh Tablets	T, LR
Bromocriptine Mesylate Capsules	T, LR
Bromocriptine Mesylate Tablets	T, LR
Brompheniramine Maleate Tablets	T
Bumetanide Tablets	T, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Bupropion Hydrochloride Tablets, Extended-Release	W
Buspirone Hydrochloride Tablets	T, LR
Busulfan Tablets	W
Butabarbital Sodium Tablets	W
Butalbital, Acetaminophen, and Caffeine Capsules	T
Butalbital, Acetaminophen, and Caffeine Tablets	T
Butalbital and Aspirin Tablets	T
Butalbital, Aspirin, and Caffeine Capsules	T
Butalbital, Aspirin, and Caffeine Tablets	T
Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules	T, LR
Cabergoline Tablets	T, LR
Calcifediol Capsules	T, LR
Calcium with Vitamin D Tablets	T, LR
Calcium Acetate Tablets	W
Calcium Carbonate Tablets	W
Calcium Carbonate and Magnesia Tablets	W
Calcium Carbonate and Magnesia Chewable Tablets	W
Calcium Citrate Tablets	W
Calcium and Magnesium Carbonates Tablets	W
Calcium Gluconate Tablets	W
Calcium Lactate Tablets	T
Calcium Pantothenate Tablets	T
Calcium Phosphate, Dibasic Tablets	W
Capecitabine Tablets	T
Captopril Tablets	T
Captopril and Hydrochlorothiazide Tablets	T
Carbamazepine Tablets	T
Carbamazepine Tablets, Extended-Release	T
Carbenicillin Indanyl Sodium Tablets	T
Carbidopa and Levodopa Tablets	W, LR
Carbinoxamine Maleate Tablets	T, LR
Urea C14 Capsules	T
Carboxymethylcellulose Sodium Tablets	T
Carisoprodol Tablets	W
Carisoprodol and Aspirin Tablets	W
Carisoprodol, Aspirin, and Codeine Phosphate Tablets	W
Carprofen Tablets	T
Carteolol Hydrochloride Tablets	T
Carvedilol Tablets	T, LR
Cascara Tablets	T, W
Castor Oil Capsules	T
Cat's Claw Capsules	T, LR
Cat's Claw Tablets	T, LR
Cefaclor Capsules	T
Cefaclor Tablets, Chewable	T
Cefaclor Tablets, Extended-Release	T, LR
Cefadroxil Capsules	T
Cefadroxil Tablets	T
Cefdinir Capsules	T, LR
Cefixime Tablets	T
Cefpodoxime Proxetil Tablets	T
Cefprozil Tablets	T
Cefuroxime Axetil Tablets	W
Cephalexin Capsules	T
Cephalexin Tablets	T
Cephadrine Capsules	T
Cephadrine Tablets	T

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Cetirizine Hydrochloride Tablets	W
Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Tablets, Extended-Release	W
Chloral Hydrate Capsules	T
Chlorambucil Tablets	W, LR
Chloramphenicol Capsules	T
Chloramphenicol Tablets	T
Chlordiazepoxide Tablets	T, LR
Chlordiazepoxide and Amitriptyline Hydrochloride Tablets	T, LR
Chlordiazepoxide Hydrochloride Capsules	T, LR
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules	T, LR
Chloroquine Phosphate Tablets	W
Chlorothiazide Tablets	W
Chlorpheniramine Maleate Capsules, Extended-Release	T
Chlorpheniramine Maleate Tablets	T
Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Capsules, Extended-Release	T, LR
Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Tablets, Extended-Release	T, LR
Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Capsules, Extended-Release	T, LR
Chlorpromazine Hydrochloride Tablets	W, LR
Chlorpropamide Tablets	W
Chlortetracycline Hydrochloride Tablets	T, LR
Chlorthalidone Tablets	W
Chlorzoxazone Tablets	T
Chlorzoxazone and Acetaminophen Capsules	T
Chondroitin Sulfate Sodium Tablets	T, LR
Chromium Picolinate Tablets	W
Cimetidine Tablets	T, LR
Cilostazol Tablets	T, LR
Cinoxacin Capsules	W
Ciprofloxacin Tablets	W
Add the following:	
■Ciprofloxacin Tablets, Extended-Release	T■15 (USP36)
Citalopram Tablets	W
Clarithromycin Tablets	T
Clarithromycin Tablets, Extended-Release	W
Clemastine Fumarate Tablets	W
Clindamycin Hydrochloride Capsules	T
Clofazimine Capsules	W
Clofibrate Capsules	W, LR
Clomiphene Citrate Tablets	W
Clomipramine Hydrochloride Capsules	W
Clonazepam Tablets	T, LR
Clonazepam Tablets, Orally Disintegrating	W, LR
Clonidine Hydrochloride Tablets	W
Clonidine Hydrochloride and Chlorthalidone Tablets	W
Clopidogrel Tablets	W
Clorazepate Dipotassium Tablets	T, LR
Clotrimazole Tablets, Vaginal	W
Red Clover Tablets	T, LR
Cloxacillin Sodium Capsules	T
Clozapine Tablets	W
Cyanocobalamin Co 57 Capsules	W, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Cyanocobalamin Co 58 Capsules	W, LR
Cocaine Hydrochloride Tablets for Topical Solution	W, LR
Codeine Phosphate Tablets	W, LR
Codeine Sulfate Tablets	W
Colectipol Hydrochloride Tablets	T
Cortisone Acetate Tablets	W
Cromolyn Sodium for Inhalation (in Capsules)	T, LR
<i>Cryptocodinium cohnii</i> Oil Capsules	T, LR
Curcuminoids Capsules	W, LR
Curcuminoids Tablets	W, LR
Cyclizine Hydrochloride Tablets	T, LR
Cyclobenzaprine Hydrochloride Tablets	W
Cyclophosphamide Tablets	T
Cycloserine Capsules	T
Cyclosporine Capsules	T
Cyproheptadine Hydrochloride Tablets	W
Danazol Capsules	W
Dantrolene Sodium Capsules	T
Dapsone Tablets	W, LR
Dehydrocholic Acid Tablets	W
Demeclocycline Hydrochloride Capsules	T, LR
Demeclocycline Hydrochloride Tablets	T, LR
Desipramine Hydrochloride Tablets	T
Desogestrel and Ethinyl Estradiol Tablets	W
Dexamethasone Tablets	W
Dexchlorpheniramine Maleate Tablets	T
Dextroamphetamine Sulfate Capsules	T
Dextroamphetamine Sulfate Tablets	W
Diazepam Capsules	T, LR
Diazepam Capsules, Extended-Release	T, LR
Diazepam Tablets	T, LR
Diazoxide Capsules	W
Dichlorphenamide Tablets	W
Diclofenac Potassium Tablets	T, LR
Diclofenac Sodium Tablets, Delayed-Release	T, LR
Diclofenac Sodium Tablets, Extended-Release	W
Dicloxacillin Sodium Capsules	T
Dicyclomine Hydrochloride Capsules	W
Dicyclomine Hydrochloride Tablets	W
Add the following:	
▲Didanosine Capsules, Delayed-Release	W▲USP36
Didanosine Tablets for Oral Suspension	T
Diethylcarbamazine Citrate Tablets	T
Diethylpropion Hydrochloride Tablets	W
Diethylstilbestrol Tablets	W
Diffunisal Tablets	W
Digitalis Capsules	T
Digitalis Tablets	T
Digitoxin Tablets	W
Digoxin Tablets	T
Dihydrotachysterol Capsules	W, LR
Dihydrotachysterol Tablets	W, LR
Dihydroxyaluminum Sodium Carbonate Tablets	W
Diltiazem Hydrochloride Tablets	T, LR
Diltiazem Hydrochloride Capsules, Extended-Release	T
Dimenhydrinate Tablets	W

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Add the following:	
■Diphenhydramine Citrate and Ibuprofen Tablets	T, LR (USP36)
Diphenhydramine Hydrochloride Capsules	T
Diphenhydramine and Pseudoephedrine Capsules	T
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets	W, LR
Dipyridamole Tablets	T, LR
Dirithromycin Tablets, Delayed-Release	T
Disopyramide Phosphate Capsules	W
Disopyramide Phosphate Capsules, Extended-Release	W
Disulfiram Tablets	T, LR
Divalproex Sodium Capsules, Delayed-Release	T, LR
Divalproex Sodium Tablets, Delayed-Release	T, LR
Divalproex Sodium Tablets, Extended-Release	W
Docusate Calcium Capsules	T
Docusate Potassium Capsules	T
Docusate Sodium Capsules	T
Docusate Sodium Tablets	W
Dolasetron Mesylate Tablets	W
Donepezil Hydrochloride Tablets	W
Donepezil Hydrochloride Tablets, Orally Disintegrating	W
Doxazosin Tablets	T
Doxepin Hydrochloride Capsules	W
Doxycycline Capsules	T, LR
Doxycycline Hyclate Capsules	T, LR
Doxycycline Hyclate Capsules, Delayed-Release	T, LR
Doxycycline Hyclate Tablets	T, LR
Doxycycline Hyclate Tablets, Delayed-Release	T, LR
Add the following:	
▲Doxycycline Tablets	T, LR (USP36)
Doxylamine Succinate Tablets	W, LR
Dronabinol Capsules	W, LR
Drospirenone and Ethinyl Estradiol Tablets	W
Duloxetine Capsules, Delayed-Release	T
Dydrogesterone Tablets	W
Dyphylline Tablets	T
Dyphylline and Guaifenesin Tablets	T
Efavirenz Capsules	W
Enalapril Maleate Tablets	W
Enalapril Maleate and Hydrochlorothiazide Tablets	W
Entacapone Tablets	LR
Ephedrine Sulfate Capsules	T, LR
Ergocalciferol Capsules	T, LR
Ergocalciferol Tablets	T, LR
Ergoloid Mesylates Capsules	T, LR
Ergoloid Mesylates Tablets	T, LR
Ergoloid Mesylates Tablets, Sublingual	T, LR
Ergonovine Maleate Tablets	W
Ergotamine Tartrate Tablets	W, LR
Ergotamine Tartrate Tablets, Sublingual	W, LR
Ergotamine Tartrate and Caffeine Tablets	W, LR
Erythromycin Capsules, Delayed-Release	T
Erythromycin Tablets	T
Erythromycin Tablets, Delayed-Release	T
Erythromycin Estolate Capsules	T
Erythromycin Estolate Tablets	T

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Erythromycin Ethylsuccinate Tablets	T
Erythromycin Stearate Tablets	T
Escitalopram Tablets	W
Esomeprazole Magnesium Capsules, Delayed-Release	T
Estazolam Tablets	T, LR
Estradiol Tablets	T, LR
Estradiol and Norethindrone Acetate Tablets	W
Estrogens Tablets, Conjugated	W
Estrogens Tablets, Esterified	W
Estropipate Tablets	W
Ethacrynic Acid Tablets	W
Ethambutol Hydrochloride Tablets	W
Ethchlorvynol Capsules	T, LR
Ethinyl Estradiol Tablets	W
Ethionamide Tablets	W
Ethosuximide Capsules	T
Ethotoin Tablets	T
Ethinodiol Diacetate and Ethinyl Estradiol Tablets	W
Ethinodiol Diacetate and Mestranol Tablets	W
Etidronate Disodium Tablets	T
Etodolac Capsules	T
Etodolac Tablets	T
Etodolac Tablets, Extended-Release	W
Famotidine Tablets	W, LR
Felbamate Tablets	W
Felodipine Tablets, Extended-Release	T
Fenofibrate Capsules	W
Fenofibrate Tablets	W
Fenoprofen Calcium Capsules	W
Fenoprofen Calcium Tablets	W
Ferrous Fumarate Tablets	T
Ferrous Fumarate and Docusate Sodium Tablets, Extended-Release	W
Ferrous Gluconate Capsules	T
Ferrous Gluconate Tablets	T
Ferrous Sulfate Tablets	T
Fexofenadine Hydrochloride Capsules	T, LR
Fexofenadine Hydrochloride Tablets	W
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Tablets, Extended-Release	W
Finasteride Tablets	T, LR
Fish Oil Containing Omega-3 Acids Capsules	T, LR
Fish Oil Containing Omega-3 Acids Capsules, Delayed-Release	T, LR
Flavoxate Hydrochloride Tablets	W, LR
Flecainide Acetate Tablets	W
Fluconazole Tablets	W
Flucytosine Capsules	T, LR
Fludrocortisone Acetate Tablets	W
Fluoxetine Capsules	T, LR
Fluoxetine Capsules, Delayed-Release	T
Fluoxetine Tablets	T
Fluoxymesterone Tablets	W
Fluphenazine Hydrochloride Tablets	T, LR
Flurazepam Hydrochloride Capsules	T, LR
Flurbiprofen Tablets	W
Flutamide Capsules	W, LR
Fluvastatin Capsules	T, LR
Fluvoxamine Maleate Tablets	T
Folic Acid Tablets	W

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Fosinopril Sodium Tablets	T
Fosinopril Sodium and Hydrochlorothiazide Tablets	T
Furazolidone Tablets	T, LR
Furosemide Tablets	W, LR
Gabapentin Capsules	W
Gabapentin Tablets	W
Galantamine Tablets	W
Garlic Tablets, Delayed-Release	T
Gemfibrozil Capsules	T
Gemfibrozil Tablets	T
Ginger Capsules	W
Ginkgo Capsules	T, LR
Ginkgo Tablets	T, LR
American Ginseng Capsules	T, LR
American Ginseng Tablets	T, LR
Asian Ginseng Capsules	T, LR
Asian Ginseng Tablets	T, LR
Glimepiride Tablets	W
Glipizide Tablets	T
Glipizide and Metformin Hydrochloride Tablets	W
Glucosamine Tablets	T, LR
Glucosamine and Chondroitin Sulfate Tablets	T, LR
Glucosamine and Methylsulfonylmethane Tablets	T, LR
Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets	T, LR
Glyburide Tablets	W
Glyburide and Metformin Hydrochloride Tablets	T, LR
Glycopyrrolate Tablets	T
Granisetron Hydrochloride Tablets	W, LR
Griseofulvin Capsules	T
Griseofulvin Tablets	T
Griseofulvin Tablets, Ultramicrosize	W
Guaifenesin Capsules	T
Guaifenesin Tablets	T
Guaifenesin and Pseudoephedrine Hydrochloride Capsules	T, LR
Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules	T, LR
Guanabenz Acetate Tablets	T, LR
Guanadrel Sulfate Tablets	T, LR
Guanethidine Monosulfate Tablets	W
Guanfacine Tablets	T, LR
Guggul Tablets	W, LR
Halazone Tablets for Solution	T, LR
Haloperidol Tablets	T, LR
Hexylresorcinol Lozenges	W
Homatropine Methylbromide Tablets	T, LR
Hydralazine Hydrochloride Tablets	T, LR
Hydrochlorothiazide Capsules	W
Hydrochlorothiazide Tablets	W
Hydrocodone Bitartrate Tablets	T, LR
Hydrocodone Bitartrate and Acetaminophen Tablets	T, LR
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	T, LR
Hydrocortisone Tablets	W
Hydroflumethiazide Tablets	T
Hydromorphone Hydrochloride Tablets	T, LR
Hydroxychloroquine Sulfate Tablets	T, LR
Hydroxyurea Capsules	T
Hydroxyzine Hydrochloride Tablets	T

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Hydroxyzine Pamoate Capsules	W
Hyoscyamine Tablets	W, LR
Hyoscyamine Sulfate Tablets	T, LR
Ibuprofen Tablets	W
Ibuprofen and Pseudoephedrine Hydrochloride Tablets	T
Imipramine Hydrochloride Tablets	T
Indapamide Tablets	W
Indomethacin Capsules	W
Indomethacin Capsules, Extended-Release	W
Sodium Iodide I 123 Capsules	W
Sodium Iodide I 131 Capsules	W
Iodoquinol Tablets	W
Iopanoic Acid Tablets	T, LR
Iopodate Sodium Capsules	T
Irbesartan Tablets	W
Irbesartan and Hydrochlorothiazide Tablets	W
Isoniazid Tablets	W, LR
Isopropamide Iodide Tablets	W
Isoproterenol Hydrochloride Tablets	W, LR
Isosorbide Dinitrate Capsules, Extended-Release	W
Isosorbide Dinitrate Tablets	W
Isosorbide Dinitrate Tablets, Chewable	W
Isosorbide Dinitrate Tablets, Extended-Release	W
Isosorbide Dinitrate Tablets, Sublingual	W
Isosorbide Mononitrate Tablets	T
Isosorbide Mononitrate Tablets, Extended-Release	T
Isotretinoin Capsules	T
Isoxsuprine Hydrochloride Tablets	T
Isradipine Capsules	T
Ivermectin Tablets	W
Ivermectin and Pyrantel Pamoate Tablets	T, LR
Kanamycin Sulfate Capsules	T
Ketoconazole Tablets	W
Ketoprofen Capsules, Extended-Release	T
Ketorolac Tromethamine Tablets	W
Labetalol Hydrochloride Tablets	T, LR
Lamivudine and Zidovudine Tablets	W, LR
Lamotrigine Tablets	W
Lamotrigine Tablets for Oral Suspension	T, LR
Lansoprazole Capsules, Delayed-Release	T
Leflunomide Tablets	T, LR
Letrozole Tablets	T
Leucovorin Calcium Tablets	W, LR
Levamisole Hydrochloride Tablets	W
Levetiracetam Tablets	T
Levocarnitine Tablets	T
Levodopa Capsules	T, LR
Levodopa Tablets	T, LR
Levonorgestrel and Ethinyl Estradiol Tablets	W
Livorphanol Tartrate Tablets	W
Levothyroxine Sodium Tablets	T, LR
Lincomycin Hydrochloride Capsules	T
Alpha Lipoic Acid Capsules	W
Alpha Lipoic Acid Tablets	W
Liothyronine Sodium Tablets	T
Liotrix Tablets	T
Lisinopril Tablets	T
Lisinopril and Hydrochlorothiazide Tablets	W

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Lithium Carbonate Capsules	W
Lithium Carbonate Tablets	W
Lithium Carbonate Tablets, Extended-Release	W
Loperamide Hydrochloride Capsules	W
Loracarbef Capsules	W
Loratadine Tablets	T
Loratadine Tablets, Orally Disintegrating	T
Lorazepam Tablets	T, LR
Losartan Potassium Tablets	T, LR
Losartan Potassium and Hydrochlorothiazide Tablets	T, LR
Lovastatin Tablets	W
Loxapine Capsules	T
Lysine Hydrochloride Tablets	W
Magaldrate Tablets	W
Magaldrate and Simethicone Tablets	W
Magnesia Tablets	W
Magnesia and Alumina Tablets	W
Magnesium Gluconate Tablets	W
Magnesium Oxide Capsules	W
Magnesium Oxide Tablets	W
Magnesium Salicylate Tablets	T
Magnesium Trisilicate Tablets	W
Maprotiline Hydrochloride Tablets	W
Mazindol Tablets	T
Mebendazole Tablets	W
Mecamylamine Hydrochloride Tablets	W
Mecizine Hydrochloride Tablets	W
Meclofenamate Sodium Capsules	T, LR
Medroxyprogesterone Acetate Tablets	W
Mefenamic Acid Capsules	T
Mefloquine Hydrochloride Tablets	T, LR
Megestrol Acetate Tablets	W
Add the following:	
▲Melatonin Tablets	T, LR▲ <i>usp36</i>
Meloxicam Tablets	W
Melphalan Tablets	W, LR
Menadiol Sodium Diphosphate Tablets	W, LR
Meperidine Hydrochloride Tablets	W, LR
Mephénytoin Tablets	W
Mephobarbital Tablets	W
Meprobamate Tablets	W
Mercaptopurine Tablets	W
Mesalamine Capsules, Extended-Release	T, LR
Mesalamine Tablets, Delayed-Release	T
Mesoridazine Besylate Tablets	W, LR
Metaproterenol Sulfate Tablets	W, LR
Metformin Hydrochloride Tablets	T
Metformin Hydrochloride Tablets, Extended-Release	W, LR
Methacycline Hydrochloride Capsules	T, LR
Methadone Hydrochloride Tablets	W
Methamphetamine Hydrochloride Tablets	T, LR
Methazolamide Tablets	W
Methdilazine Hydrochloride Tablets	T, LR
Methenamine Tablets	W
Methenamine Hippurate Tablets	W
Methenamine Mandelate Tablets	W
Methenamine Mandelate Tablets, Delayed-Release	W

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Methimazole Tablets	W, LR
Methocarbamol Tablets	T
Methotrexate Tablets	W
Methoxsalen Capsules	T, LR
Methscopolamine Bromide Tablets	T
Methsuximide Capsules	T
Methyclothiazide Tablets	W
Methylcellulose Tablets	W
Methyldopa Tablets	W
Methyldopa and Chlorothiazide Tablets	W
Methyldopa and Hydrochlorothiazide Tablets	W
Methylergonovine Maleate Tablets	T, LR
Methylphenidate Hydrochloride Tablets	T
Methylphenidate Hydrochloride Tablets, Extended-Release	T
Methylprednisolone Tablets	T
Methylsulfonylmethane Tablets	T, LR
Methyltestosterone Capsules	W
Methyltestosterone Tablets	W
Methysergide Maleate Tablets	T
Metoclopramide Tablets	T, LR
Metolazone Tablets	T, LR
Metoprolol Succinate Tablets, Extended-Release	T
Metoprolol Tartrate Tablets	T, LR
Metoprolol Tartrate and Hydrochlorothiazide Tablets	T, LR
Metronidazole Capsules	W, LR
Metronidazole Tablets	W, LR
Metyrapone Tablets	T, LR
Metyrosine Capsules	W
Mexiletine Hydrochloride Capsules	T
Midodrine Hydrochloride Tablets	W
Minerals Capsules	T, LR
Minerals Tablets	T, LR
Minocycline Hydrochloride Capsules	T, LR
Minocycline Hydrochloride Tablets	T, LR
Minoxidil Tablets	T
Mirtazapine Tablets	T, LR
Mirtazapine Tablets, Orally Disintegrating	LR
Mitotane Tablets	T, LR
Modafinil Tablets	T
Molindone Hydrochloride Tablets	T, LR
Moricizine Hydrochloride Tablets	T
Morphine Sulfate Capsules, Extended-Release	T, LR
Mycophenolate Mofetil Capsules	W, LR
Mycophenolate Mofetil Tablets	W, LR
Nabumetone Tablets	W
Nadolol Tablets	T
Nadolol and Bendroflumethiazide Tablets	T
Nafcillin Sodium Capsules	T
Nafcillin Sodium Tablets	T, LR
Nalidixic Acid Tablets	T
Naltrexone Hydrochloride Tablets	T
Naproxen Tablets	W
Naproxen Tablets, Delayed-Release	W
Naproxen Sodium Tablets	W
Naratriptan Tablets	T
Nateglinide Tablets	T
Nefazodone Hydrochloride Tablets	T
Neomycin Sulfate Tablets	T

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Neostigmine Bromide Tablets	T
Nevirapine Tablets	W
Niacin Tablets	W
Niacin Tablets, Extended-Release	T
Niacinamide Tablets	T
Nifedipine Capsules	T, LR
Nifedipine Tablets, Extended-Release	T, LR
Nitrofurantoin Capsules	T
Nitrofurantoin Tablets	T, LR
Nitroglycerin Tablets	T
Nitroglycerin Tablets, Sublingual	T
Norethindrone Tablets	W
Norethindrone and Ethinyl Estradiol Tablets	W
Norethindrone and Mestranol Tablets	W
Norethindrone Acetate Tablets	W
Norethindrone Acetate and Ethinyl Estradiol Tablets	W
Norfloxacin Tablets	W
Norgestimate and Ethinyl Estradiol Tablets	W
Norgestrel Tablets	W
Norgestrel and Ethinyl Estradiol Tablets	W
Nortriptyline Hydrochloride Capsules	T
Nystatin Tablets	T, LR
Nystatin Tablets, Vaginal	W, LR
Ofloxacin Tablets	W
Olanzapine Tablets	T, LR
Olanzapine and Fluoxetine Capsules	T
Oleovitamin A and D Capsules	T, LR
Omega-3 Acids Ethyl Esters Capsules	T, LR
Omeprazole Capsules, Delayed-Release	T, LR
Ondansetron Tablets	T, LR
Ondansetron Tablets, Orally Disintegrating	LR
Orbifloxacin Tablets	T
Orlistat Capsules	T
Orphenadrine Citrate Tablets, Extended-Release	T, LR
Osetamivir Phosphate Capsules	W
Oxacillin Sodium Capsules	T
Oxandrolone Tablets	T, LR
Oxaprozin Tablets	T, LR
Oxazepam Capsules	W
Oxazepam Tablets	W
Oxprenolol Hydrochloride Tablets	W, LR
Oxprenolol Hydrochloride Tablets, Extended-Release	W, LR
Oxtriphylline Tablets	T
Oxtriphylline Tablets, Delayed-Release	T
Oxtriphylline Tablets, Extended-Release	T
Oxybutynin Chloride Tablets	T, LR
Oxybutynin Chloride Tablets, Extended-Release	T
Oxycodone Hydrochloride Tablets	T, LR
Oxycodone Hydrochloride Tablets, Extended-Release	T, LR
Oxycodone and Acetaminophen Capsules	T, LR
Oxycodone and Acetaminophen Tablets	T, LR
Oxycodone and Aspirin Tablets	T, LR
Oxymetholone Tablets	W
Oxytetracycline Tablets	T, LR
Oxytetracycline and Nystatin Capsules	T, LR
Oxytetracycline Hydrochloride Capsules	T, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Oxytetracycline Hydrochloride and Polymyxin B Sulfate Tablets, Vaginal	W
Pancreatin Tablets	T
Pancrelipase Capsules	T
Pancrelipase Capsules, Delayed-Release	T
Pancrelipase Tablets	T
Pantoprazole Sodium Tablets, Delayed-Release	W
Papain Tablets for Topical Solution	T, LR
Papaverine Hydrochloride Tablets	T
Paromomycin Sulfate Capsules	T
Paroxetine Tablets	T
Penbutolol Sulfate Tablets	W, LR
Penicillamine Capsules	T
Penicillamine Tablets	T
Penicillin G Benzathine Tablets	T
Penicillin G Potassium Tablets	T
Penicillin V Tablets	T
Penicillin V Potassium Tablets	T
Pentazocine and Acetaminophen Tablets	T, LR
Pentazocine and Aspirin Tablets	T, LR
Pentazocine and Naloxone Tablets	T, LR
Pentoxifylline Tablets, Extended-Release	W
Perphenazine Tablets	T, LR
Perphenazine and Amitriptyline Hydrochloride Tablets	W
Phenazopyridine Hydrochloride Tablets	T
Phendimetrazine Tartrate Capsules	T
Phendimetrazine Tartrate Tablets	W
Phenelzine Sulfate Tablets	T
Phenmetrazine Hydrochloride Tablets	T
Phenobarbital Tablets	W
Phenoxybenzamine Hydrochloride Capsules	W
Phensuximide Capsules	T
Phentermine Hydrochloride Capsules	T
Phentermine Hydrochloride Tablets	T
Phenylbutazone Tablets	T
Phenylpropanolamine Hydrochloride Capsules	T, LR
Phenylpropanolamine Hydrochloride Capsules, Extended-Release	T, LR
Phenylpropanolamine Hydrochloride Tablets	T, LR
Phenylpropanolamine Hydrochloride Tablets, Extended-Release	T, LR
Phenytoin Tablets	W
Phenytoin Sodium Capsules, Extended	T
Phenytoin Sodium Capsules, Prompt	T
Phytonadione Tablets	W, LR
Pilocarpine Hydrochloride Tablets	T
Pimozide Tablets	T, LR
Pindolol Tablets	W, LR
Pioglitazone Tablets	T
Piperazine Citrate Tablets	T
Piroxicam Capsules	T, LR
Potassium Bicarbonate Effervescent Tablets for Oral Solution	T
Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution	T
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution	T
Potassium Chloride Capsules, Extended-Release	T
Potassium Chloride Tablets, Extended-Release	T

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution	T
Potassium Citrate Tablets	W
Potassium Citrate Tablets, Extended-Release	T
Potassium Gluconate Tablets	T
Potassium Iodide Tablets	T
Potassium Iodide Tablets, Delayed-Release	T
Potassium Perchlorate Capsules	T, LR
Pravastatin Sodium Tablets	T
Praziquantel Tablets	T
Prazosin Hydrochloride Capsules	W, LR
Prednisolone Tablets	W
Prednisone Tablets	W
Primaquine Phosphate Tablets	W, LR
Primidone Tablets	W
Probenecid and Colchicine Tablets	W, LR
Probuco Tablets	W, LR
Procainamide Hydrochloride Capsules	T
Procainamide Hydrochloride Tablets	T
Procarbazine Hydrochloride Capsules	T, LR
Prochlorperazine Maleate Tablets	W
Procydine Hydrochloride Tablets	T
Promazine Hydrochloride Tablets	T, LR
Promethazine Hydrochloride Tablets	T, LR
Propantheline Bromide Tablets	W
Propoxyphene Hydrochloride Capsules	T
Propoxyphene Hydrochloride and Acetaminophen Tablets	T
Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules	T
Propoxyphene Napsylate Tablets	T
Propoxyphene Napsylate and Acetaminophen Tablets	T
Propoxyphene Napsylate and Aspirin Tablets	T
Propranolol Hydrochloride Capsules, Extended-Release	W
Propranolol Hydrochloride Tablets	W, LR
Propranolol Hydrochloride and Hydrochlorothiazide Capsules, Extended-Release	W
Propranolol Hydrochloride and Hydrochlorothiazide Tablets	W
Propylthiouracil Tablets	W
Protriptyline Hydrochloride Tablets	T
Pseudoephedrine Hydrochloride Tablets	T
Pseudoephedrine Hydrochloride Tablets, Extended-Release	T
Pygeum Capsules	T
Pyrazinamide Tablets	W
Pyridostigmine Bromide Tablets	T
Pyridoxine Hydrochloride Tablets	W
Pyrilamine Maleate Tablets	W
Pyrimethamine Tablets	T, LR
Pyriminyl Pamoate Tablets	T, LR
Quazepam Tablets	W
Quinapril Tablets	W
Add the following:	
■Quinapril and Hydrochlorothiazide Tablets	W, LR, ¹⁵ (USP36)
Quinidine Gluconate Tablets, Extended-Release	W, LR
Quinidine Sulfate Capsules	T, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Quinidine Sulfate Tablets	W, LR
Quinidine Sulfate Tablets, Extended-Release	W, LR
Quinine Sulfate Capsules	T
Quinine Sulfate Tablets	W
Raloxifene Hydrochloride Tablets	T
Ramipril Capsules	W
Ranitidine Tablets	T, LR
Rauwolfia Serpentina Tablets	T, LR
Reserpine Tablets	T, LR
Reserpine and Chlorothiazide Tablets	T, LR
Reserpine, Hydralazine Hydrochloride, and Hydrochlorothiazide Tablets	T, LR
Reserpine and Hydrochlorothiazide Tablets	T, LR
Add the following:	
■Ribavirin Capsules	W, ¹⁵ (USP36)
Ribavirin Tablets	T
Riboflavin Tablets	T, LR
Rifabutin Capsules	W
Rifampin Capsules	T, LR
Rifampin and Isoniazid Capsules	T, LR
Rifampin, Isoniazid, and Pyrazinamide Tablets	T, LR
Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets	T, LR
Riluzole Tablets	W, LR
Rimantadine Hydrochloride Tablets	T, LR
Risedronate Sodium Tablets	W
Risperidone Tablets, Orally Disintegrating	W, LR
Risperidone Tablets	T, LR
Ritodrine Hydrochloride Tablets	T
Rivastigmine Tartrate Capsules	T
Ropinirole Tablets	W
Add the following:	
▲Rufinamide Tablets	T, ¹⁵ (USP36)
Saccharin Sodium Tablets	W
Salsalate Capsules	T
Salsalate Tablets	T
Saquinavir Capsules	T
Saw Palmetto Capsules	T, LR
Schizochytrium Oil Capsules	T, LR
Scopolamine Hydrobromide Tablets	T, LR
Secobarbital Sodium Capsules	T
Secobarbital Sodium and Amobarbital Sodium Capsules	W
Selegiline Hydrochloride Tablets	T, LR
Sennosides Tablets	W
Sertraline Tablets	W
Simethicone Capsules	W
Simethicone Tablets	W
Simvastatin Tablets	T
Sodium Bicarbonate Tablets	W
Sodium Chloride Tablets	W
Sodium Chloride Tablets for Solution	W
Sodium Chloride and Dextrose Tablets	W
Sodium Fluoride Tablets	T
Sodium Salicylate Tablets	W
Sotalol Hydrochloride Tablets	W, LR
Soy Isoflavones Capsules	T, LR
Soy Isoflavones Tablets	T, LR
Spironolactone Tablets	T, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Spironolactone and Hydrochlorothiazide Tablets	T, LR
Stanozolol Tablets	T, LR
Stavudine Capsules	T
Sulfadiazine Tablets	W, LR
Sulfadimethoxine Tablets	T, LR
Sulfadoxine and Pyrimethamine Tablets	W, LR
Sulfamethizole Tablets	W
Sulfamethoxazole Tablets	W, LR
Sulfamethoxazole and Trimethoprim Tablets	W, LR
Sulfapyridine Tablets	W, LR
Sulfasalazine Tablets	W
Sulfasalazine Tablets, Delayed-Release	W
Sulfinpyrazone Capsules	W
Sulfinpyrazone Tablets	W
Sulfisoxazole Tablets	W, LR
Sulindac Tablets	W
Sumatriptan Tablets	W
Tacrolimus Capsules	T
Add the following:	
▲Tadalafil Tablets	T▲ ^{USP36}
Tamoxifen Citrate Tablets	W, LR
Tamsulosin Hydrochloride Capsules	T
Telmisartan Tablets	W
Telmisartan and Hydrochlorothiazide Tablets	W
Temazepam Capsules	W, LR
Terazosin Capsules	W, LR
Terazosin Tablets	W, LR
Terbinafine Tablets	W, LR
Terbutaline Sulfate Tablets	T
Testolactone Tablets	T
Tetracycline Hydrochloride Capsules	T, LR
Tetracycline Hydrochloride Tablets	T, LR
Tetracycline Hydrochloride and Novobiocin Sodium Tablets	T
Tetracycline Hydrochloride, Novobiocin Sodium, and Prednisolone Tablets	T
Tetracycline Hydrochloride and Nystatin Capsules	T, LR
Thalidomide Capsules	W
Theophylline Capsules	W
Theophylline Capsules, Extended-Release	W
Theophylline Tablets	W
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets	T
Theophylline and Guaifenesin Capsules	T
Theophylline Sodium Glycinate Tablets	W
Thiabendazole Tablets	T
Thiamine Hydrochloride Tablets	T, LR
Thiethylperazine Maleate Tablets	T, LR
Thioguanine Tablets	T
Thioridazine Hydrochloride Tablets	T, LR
Thiothixene Capsules	W, LR
Thyroid Tablets	T
Ticlopidine Hydrochloride Tablets	W
Timolol Maleate Tablets	W
Timolol Maleate and Hydrochlorothiazide Tablets	W, LR
Tizanidine Tablets	T
Tocainide Hydrochloride Tablets	W
Tolazamide Tablets	T
Tolazoline Hydrochloride Tablets	W
Tolbutamide Tablets	W

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Tolcapone Tablets	T
Tolmetin Sodium Capsules	T
Tolmetin Sodium Tablets	W
Topiramate Tablets	T
Tramadol Hydrochloride Tablets	T
Tramadol Hydrochloride Tablets, Extended-Release	T
Trandolapril Tablets	T
Tranylcypromine Tablets	W
Trazodone Hydrochloride Tablets	T, LR
Triamcinolone Tablets	W
Triamterene Capsules	T, LR
Triamterene and Hydrochlorothiazide Capsules	T, LR
Triamterene and Hydrochlorothiazide Tablets	T, LR
Triazolam Tablets	T, LR
Trichlormethiazide Tablets	T
Trientine Hydrochloride Capsules	T
Trifluoperazine Hydrochloride Tablets	W, LR
Triflupromazine Hydrochloride Tablets	W, LR
Trihexyphenidyl Hydrochloride Capsules, Extended-Release	T
Trihexyphenidyl Hydrochloride Tablets	T
Trimeprazine Tartrate Tablets	W, LR
Trimethobenzamide Hydrochloride Capsules	W
Trimethoprim Tablets	T, LR
Trioxsalen Tablets	W, LR
Tripelennamine Hydrochloride Tablets	W
Triple Sulfa Tablets, Vaginal	W, LR
Tripolidine Hydrochloride Tablets	T, LR
Tripolidine and Pseudoephedrine Hydrochlorides Tablets	T, LR
Trisulfapyrimidines Tablets	W
Troleandomycin Capsules	T
Add the following:	
▲Tropium Chloride Tablets	T, LR▲ ^{USP36}
Ubidecarenone Capsules	T, LR
Ubidecarenone Tablets	T, LR
Ursodiol Capsules	W
Ursodiol Tablets	W
Valacyclovir Tablets	T
Valerian Tablets	T, LR
Valganciclovir Tablets	T
Valproic Acid Capsules	T
Valsartan Tablets	T
Valsartan and Hydrochlorothiazide Tablets	T
Vancomycin Hydrochloride Capsules	T
Venlafaxine Tablets	W
Verapamil Hydrochloride Capsules, Extended-Release	T, LR
Verapamil Hydrochloride Tablets	T, LR
Verapamil Hydrochloride Tablets, Extended-Release	T, LR
Vitamin A Capsules	T, LR
Vitamin A Tablets	T, LR
Vitamin E Capsules	T
Oil-Soluble Vitamins Capsules	T, LR
Oil-Soluble Vitamins Tablets	T, LR
Add the following:	
▲Oil-Soluble Vitamins with Minerals Capsules	T, LR▲ ^{USP36}

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Add the following:	
▲Oil-Soluble Vitamins with Minerals Tablets	T, LR▲ <i>USP36</i>
Oil- and Water-Soluble Vitamins Capsules	T, LR
Oil- and Water-Soluble Vitamins Tablets	T, LR
Oil- and Water-Soluble Vitamins with Minerals Capsules	T, LR
Oil- and Water-Soluble Vitamins with Minerals Tablets	T, LR
Water-Soluble Vitamins Capsules	T, LR
Water-Soluble Vitamins Tablets	T, LR
Water-Soluble Vitamins with Minerals Capsules	T, LR
Water-Soluble Vitamins with Minerals Tablets	T, LR

Container Specifications for Capsules and Tablets (Continued)

Monograph Title	Container Specification
Warfarin Sodium Tablets	T, LR
Zalcitabine Tablets	T, LR
Zaleplon Capsules	LR
Zidovudine Capsules	T, LR
Zidovudine Tablets	T, LR
Zinc Citrate Tablets	W
Zinc Gluconate Tablets	T, LR
Zinc Sulfate Tablets	W
Zolpidem Tartrate Tablets	W
Zolpidem Tartrate Tablets, Extended-Release	W
Zonisamide Capsules	T, LR

DESCRIPTION AND SOLUBILITY

Description and Relative Solubility of USP and NF Articles

The “description” and “solubility” statements pertaining to an article (formerly included in the individual monograph) are general in nature. The information is provided for those who use, prepare, and dispense drugs, solely to indicate descriptive and solubility properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of the integrity of an article.

Taste and Odor

Organoleptic characteristics are indicated in many instances because they may be useful and descriptive properties of substances. However, they are not meant to be applied as tests for identifying materials.

The inclusion of odor or taste among other descriptive properties may aid in identifying the causative agent following accidental exposure to or contact with a substance. This information is provided as a warning or to make an individual aware of sensations that may be encountered. The use of odor or taste as a test for identification or content is strongly discouraged.

The characteristic odor of a volatile substance becomes apparent immediately on opening a container of it. The odor may be agreeable (e.g., Peppermint Oil), unpleasant (e.g., Sulfur Dioxide), or potentially hazardous on prolonged exposure (e.g., Coal Tar). Moreover, an unexpected odor may be encountered if the characteristics of a substance are not known or if a container is incorrectly labeled. Consequently, containers of such substances should be opened cautiously, preferably in a well-ventilated fume hood. A characteristic taste or sensation produced in the oral cavity likewise is apparent if traces of residue materials on fingers are inadvertently brought into contact with the tongue or adjacent mucosal tissues.

Solubility

Only where a special, quantitative solubility test is given in the individual monograph, and is designated by a test heading, is it a test for purity.

The approximate solubilities of Pharmacopeial and National Formulary substances are indicated by the descriptive terms in the accompanying table. The term “miscible” as used in this Pharmacopeia pertains to a substance that yields a homogeneous mixture when mixed in any proportion with the designated solvent.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

Soluble Pharmacopeial and National Formulary articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers,

and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

Abacavir Sulfate: White to off-white powder. Soluble in water, in ethyl acetate, in absolute alcohol, and in methanol.

Acacia: Is practically odorless and produces a mucilaginous sensation on the tongue. Insoluble in alcohol. Optical rotation varies depending on the source of Acacia. For example, specific rotation values, calculated on the anhydrous basis and determined on a 1.0% (w/v) solution, usually are between -25° and -35° for *Acacia senegal* and between $+35^{\circ}$ and $+60^{\circ}$ for *Acacia seyal*. *NF category:* Emulsifying and/or solubilizing agent; suspending and/or viscosity-increasing agent; tablet binder.

Acebutolol Hydrochloride: White or almost white, crystalline powder. Soluble in alcohol and in water; very slightly soluble in acetone and in methylene chloride; practically insoluble in ether. Melts at about 141° to 144° .

Acesulfame Potassium: A white, crystalline powder or colorless crystals. Soluble in water; very slightly soluble in acetone and in alcohol. *NF category:* Sweetening agent.

Acetaminophen: White, odorless, crystalline powder, having a slightly bitter taste. Freely soluble in alcohol; soluble in boiling water and in 1 N sodium hydroxide.

Acetazolamide: White to faintly yellowish-white, crystalline, odorless powder. Sparingly soluble in practically boiling water; slightly soluble in alcohol; very slightly soluble in water.

Acetic Acid: Clear, colorless liquid, having a strong, characteristic odor, and a sharply acid taste. Specific gravity is about 1.045. Miscible with water, with alcohol, and with glycerin. *NF category:* Acidifying agent; buffering agent.

Glacial Acetic Acid: Clear, colorless liquid, having a pungent, characteristic odor and, when well diluted with water, an acid taste. Boils at about 118° . Specific gravity is about 1.05. Miscible with water, with alcohol, and with glycerin. *NF category:* Acidifying agent.

Acetohexamide: White, crystalline, practically odorless powder. Soluble in pyridine and in dilute solutions of alkali hydroxides; slightly soluble in alcohol and in chloroform; practically insoluble in water and in ether.

Acetohydroxamic Acid: White, slightly hygroscopic, crystalline powder. Melts, after drying at about 80° for 2 to 4 hours, at about 88° . Freely soluble in water and in alcohol; very slightly soluble in chloroform.

Acetone: Transparent, colorless, mobile, volatile liquid, having a characteristic odor. A solution (1 in 2) is neutral to litmus. Miscible with water, with alcohol, with ether, with chloroform, and with most volatile oils. *NF category:* Solvent.

Acetylcholine Chloride: White or off-white crystals or crystalline powder. Very soluble in water; freely soluble in alcohol; insoluble in ether. Is decomposed by hot water and by alkalies.

Acetylcysteine: White, crystalline powder, having a slight acetic odor. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Acetyltributyl Citrate: Clear, practically colorless, oily liquid. Freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene; insoluble in water. *NF category:* Plasticizer.

Acetyltriethyl Citrate: Clear, practically colorless, oily liquid. Freely soluble in alcohol, in isopropyl alcohol, in ace-

tone, and in toluene; insoluble in water. *NF category*: Plasticizer.

Acitretin: Yellow or greenish, crystalline powder. Sparingly soluble in tetrahydrofuran; slightly soluble in acetone and in alcohol; very slightly soluble in cyclohexane; practically insoluble in water.

Acyclovir: White to off-white, crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in diluted hydrochloric acid; slightly soluble in water; insoluble in alcohol.

Add the following:

• **Adapalene**: White or almost white powder. Soluble in tetrahydrofuran; sparingly soluble in ethanol; practically insoluble in water. (RB 1-Dec-2012)

Ademetionine Disulfate Tosylate: White powder. Freely soluble in water.

Adenine: White crystals or crystalline powder. Is odorless and tasteless. Sparingly soluble in boiling water; slightly soluble in alcohol; very slightly soluble in water; practically insoluble in ether and in chloroform.

Adenosine: White, odorless, crystalline powder. Slightly soluble in water; practically insoluble in alcohol. Melts at about 235°.

Adipic Acid: A white, crystalline powder. Freely soluble in alcohol and in methanol; soluble in boiling water and in acetone; slightly soluble in water. *NF category*: Buffering agent.

Agar: Odorless or has a slight odor, and produces a mucilaginous sensation on the tongue. Soluble in boiling water; insoluble in cold water. *NF category*: Suspending and/or viscosity-increasing agent.

Alamic Acid: *NF category*: Suspending and/or viscosity-increasing agent.

Alanine: White, odorless crystals or crystalline powder, having a slightly sweet taste. Freely soluble in water; slightly soluble in 80% alcohol; insoluble in ether.

Albendazole: White to faintly yellowish powder. Freely soluble in anhydrous formic acid; very slightly soluble in ether and in methylene chloride; practically insoluble in alcohol and in water.

Albumin Human: Practically odorless, moderately viscous, clear, brownish fluid.

Albumin Human: Clear, slightly viscous, and colorless to yellow amber in color. *NF category*: Vehicle (sterile).

Albuterol: White, crystalline powder. Soluble in alcohol; sparingly soluble in water. Melts at about 156°.

Albuterol Sulfate: White or practically white powder. Freely soluble in water; slightly soluble in alcohol, in chloroform, and in ether.

Alcohol: Clear, colorless, mobile, volatile liquid. Has a characteristic odor and produces a burning sensation on the tongue. Is readily volatilized even at low temperatures, and boils at about 78°. Is flammable. Miscible with water and with practically all organic solvents. *NF category*: Solvent.

Dehydrated Alcohol: Clear, colorless, mobile, volatile liquid. Has a characteristic odor and produces a burning sensation on the tongue. Is readily volatilized even at low temperatures, and boils at about 78°. Is flammable. Miscible with water and with practically all organic solvents.

Diluted Alcohol: Clear, colorless, mobile liquid, having a characteristic odor and producing a burning sensation on the tongue. *NF category*: Solvent.

Rubbing Alcohol: Transparent, colorless, or colored as desired, mobile, volatile liquid. Has an extremely bitter taste and, in the absence of added odorous constituents, a characteristic odor. Is flammable.

Alendronate Sodium: White, free-flowing powder. Soluble in water; very slightly soluble in dimethyl sulfoxide, in

methyl alcohol, and in propylene glycol; practically insoluble in acetone, in acetonitrile, in alcohol, in chloroform, and in isopropyl alcohol.

Alfadex: A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; practically insoluble in ethanol and in methylene chloride.

Alfentanil Hydrochloride: White to almost white powder. Freely soluble in methanol, in alcohol, and in chloroform; soluble in water; sparingly soluble in acetone. Melting point range, crystals from acetone: 136° – 143° (anhydrous) and reported as crystals from aqueous hydrochloric acid: 116° – 126° (monohydrate).

Alfentanil Injection: Clear, colorless solution.

Alfuzosin Hydrochloride: White to almost white powder, slightly hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in methylene chloride.

Alginic Acid: White to yellowish white, fibrous powder. Is odorless, or practically odorless, and is tasteless. Soluble in alkaline solutions; insoluble in water and in organic solvents. *NF category*: Suspending and/or viscosity-increasing agent; tablet binder; tablet disintegrant.

Alkyl (C12-15) Benzoate: Clear, practically colorless, oily liquid. Soluble in acetone, in alcohol, in isopropyl alcohol, in ethyl acetate, in isopropyl myristate, in isopropyl palmitate, in lanolin, in mineral oil, in vegetable oils, and in volatile silicones; insoluble in water, in glycerin, and in propylene glycol. *NF category*: Vehicle (oleaginous); emollient.

Allantoin: White, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol. Melts at about 225°, with decomposition.

Allopurinol: Fluffy white to off-white powder, having only a slight odor. Soluble in solutions of potassium and sodium hydroxides; very slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Allyl Isothiocyanate: Colorless to pale yellow, very refractive, liquid. Pungent irritating odor, acrid taste. [Caution: Lachrymator.] Miscible with alcohol, with carbon disulfide, and with ether. Slightly soluble in water.

Almond Oil: Clear, pale straw-colored or colorless, oily liquid, having a bland taste. Remains clear at –10°, and does not congeal until cooled to almost –20°. Slightly soluble in alcohol. Miscible with ether, with chloroform, with benzene, and with solvent hexane. *NF category*: Flavors and perfumes; vehicle (oleaginous).

Aloe: Has a characteristic, somewhat sour and disagreeable, odor.

Alprazolam: A white to off-white, crystalline powder. Melts at about 225°. Freely soluble in chloroform; soluble in alcohol; sparingly soluble in acetone; slightly soluble in ethyl acetate; insoluble in water.

Alprostadil: A white to off-white, crystalline powder. Melts at about 110°. Freely soluble in alcohol; soluble in water and in acetone; slightly soluble in ethyl acetate; very slightly soluble in chloroform and in ether.

Altretamine: White, crystalline powder. Soluble in chloroform; insoluble in water.

Ammonium Alum: Large, colorless crystals, crystalline fragments, or white powder. Is odorless, and has a sweetish, strongly astringent taste. Its solutions are acid to litmus. Very soluble in boiling water; freely soluble in water; freely soluble in glycerin; insoluble in alcohol.

Potassium Alum: Large, colorless crystals, crystalline fragments, or white powder. Is odorless, and has a sweetish, strongly astringent taste. Its solutions are acid to litmus. Very soluble in boiling water; freely soluble in water; freely soluble in glycerin; insoluble in alcohol.

Aluminum Acetate Topical Solution: Clear, colorless liquid having a faint odor of acetic acid, and a sweetish, astringent taste. Specific gravity is about 1.02.

Aluminum Chloride: White, or yellowish-white, deliquescent, crystalline powder. Is practically odorless, and has a sweet, very astringent taste. Its solutions are acid to litmus. Very soluble in water; freely soluble in alcohol; soluble in glycerin.

Aluminum Hydroxide Gel: White, viscous suspension, from which small amounts of clear liquid may separate on standing.

Dried Aluminum Hydroxide Gel: White, odorless, tasteless, amorphous powder. Soluble in dilute mineral acids and in solutions of fixed alkali hydroxides; insoluble in water and in alcohol.

Aluminum Monostearate: Fine, white to yellowish-white, bulky powder, having a faint, characteristic odor. Insoluble in water, in alcohol, and in ether. *NF category:* Suspending and/or viscosity-increasing agent.

Aluminum Oxide: Occurs as a white or almost white, amorphous powder. It is very slightly soluble in dilute mineral acids and in solutions of alkali hydroxides. It is practically insoluble in water.

Aluminum Phosphate Gel: White, viscous suspension from which small amounts of water separate on standing.

Aluminum Subacetate Topical Solution: Clear, colorless or faintly yellow liquid, having an odor of acetic acid and an acid reaction to litmus. Gradually becomes turbid on standing, through separation of a more basic salt.

Aluminum Sulfate: White, crystalline powder, shining plates, or crystalline fragments. Is stable in air. Is odorless, and has a sweet taste, becoming mildly astringent. Freely soluble in water; insoluble in alcohol.

Amantadine Hydrochloride: White or practically white, crystalline powder, having a bitter taste. Freely soluble in water; soluble in alcohol and in chloroform.

Amifostine: White, crystalline powder. Freely soluble in water.

Amikacin: White, crystalline powder. Sparingly soluble in water.

Amikacin Sulfate: White, crystalline powder. Freely soluble in water.

Amiloride Hydrochloride: Yellow to greenish-yellow, odorless or practically odorless powder. Freely soluble in dimethyl sulfoxide; sparingly soluble in methanol; slightly soluble in water; insoluble in ether, in ethyl acetate, in acetone, and in chloroform.

Amino Methacrylate Copolymer: Colorless to yellowish granules. Soluble in acetone, in isopropyl alcohol, and in diluted acids; practically insoluble in water. The solutions are clear to slightly cloudy. *NF category:* Coating agent; polymer membrane; tablet binder.

Aminobenzoate Potassium: White, crystalline powder. The pH of a 1 in 100 solution in water is about 7. Very soluble in water; soluble in alcohol; practically insoluble in ether.

Aminobenzoic Acid: White or slightly yellow, odorless crystals or crystalline powder. Discolors on exposure to air or light. Freely soluble in alcohol and in solutions of alkali hydroxides and carbonates; sparingly soluble in ether; slightly soluble in water and in chloroform.

Aminobenzoic Acid Topical Solution: Straw-colored solution having the odor of alcohol.

Aminocaproic Acid: Fine, white, crystalline powder. Is odorless, or practically odorless. Its solutions are neutral to litmus. Melts at about 205°. Freely soluble in water, in acids, and in alkalis; slightly soluble in methanol and in alcohol; practically insoluble in chloroform and in ether.

Aminogluthethimide: Fine, white, or creamy white, crystalline powder. Soluble in most organic solvents; very slightly soluble in water. Forms water-soluble salts with strong acids.

Aminohippuric Acid: White, crystalline powder. Discolors on exposure to light. Melts at about 195°, with decomposition. Freely soluble in alkaline solutions, with some decomposition, and in diluted hydrochloric acid; sparingly soluble in water and in alcohol; very slightly soluble in benzene, in carbon tetrachloride, in chloroform, and in ether.

Aminopentamide Sulfate: White, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether.

Aminophylline: White or slightly yellowish granules or powder, having a slight ammoniacal odor and a bitter taste. Upon exposure to air, it gradually loses ethylenediamine and absorbs carbon dioxide with the liberation of free theophylline. Its solutions are alkaline to litmus. One g dissolves in 25 mL of water to give a clear solution; 1 g dissolved in 5 mL of water crystallizes upon standing, but redissolves when a small amount of ethylenediamine is added. Insoluble in alcohol and in ether.

Aminophylline Tablets: May have a faint ammoniacal odor.

Aminosalicylate Sodium: White to cream-colored, crystalline powder. Is practically odorless, and has a sweet, saline taste. Its solutions decompose slowly and darken in color. Freely soluble in water; sparingly soluble in alcohol; very slightly soluble in ether and in chloroform.

Aminosalicylic Acid: White or practically white, bulky powder, that darkens on exposure to light and air. Is odorless, or has a slight acetous odor. Soluble in alcohol; slightly soluble in water and in ether; practically insoluble in benzene.

Amiodarone Hydrochloride: White or almost white, fine, crystalline powder. Freely soluble in methylene chloride; soluble in methanol; sparingly soluble in alcohol; very slightly soluble in water.

Amitriptyline Hydrochloride: White or practically white, odorless or practically odorless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methanol; insoluble in ether.

Amlodipine Besylate: A white or almost white powder. Freely soluble in methanol; sparingly soluble in alcohol; slightly soluble in 2-propanol and in water.

Strong Ammonia Solution: Clear, colorless liquid, having an exceedingly pungent, characteristic odor. Specific gravity is about 0.90. *NF category:* Alkalizing agent.

Aromatic Ammonia Spirit: Practically colorless liquid when recently prepared, but gradually acquiring a yellow color on standing. Has the taste of ammonia, has an aromatic and pungent odor, and is affected by light. Specific gravity is about 0.90.

Ammonio Methacrylate Copolymer: Colorless, clear to white-opaque granules or a white powder, both with a faint amine-like odor. Soluble to freely soluble in methanol, in alcohol, and in isopropyl alcohol, each of which contains small amounts of water; soluble to freely soluble in acetone, in ethyl acetate, and in methylene chloride. The solutions are clear to slightly cloudy. Insoluble in petroleum ether and in water. *NF category:* Coating agent; tablet binder; polymer membrane.

Ammonio Methacrylate Copolymer Dispersion: Milky-white liquids of low viscosity with a faint characteristic odor. Miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy solution is obtained on mixing one part with five parts of acetone, alcohol, or isopropyl alcohol. When mixed with methanol in a ratio of 1:5, Ammonio Methacrylate Copolymer Dispersion Type A dissolves completely, and Ammonio Methacrylate Copolymer Dispersion Type B dissolves only partially. *NF category:* Coating agent; polymer membrane; tablet binder.

Ammonium Carbonate: White powder, or hard, white or translucent masses, having a strong odor of ammonia, without empyreuma, and a sharp, ammoniacal taste. Its solutions are alkaline to litmus. On exposure to air, it loses

ammonia and carbon dioxide, becoming opaque, and is finally converted into friable porous lumps or a white powder of ammonium bicarbonate. Freely soluble in water, but is decomposed by hot water. *NF category*: Alkalizing agent; buffering agent.

Ammonium Chloride: Colorless crystals or white, fine or coarse, crystalline powder. Has a cool, saline taste, and is somewhat hygroscopic. Freely soluble in water and in glycerin, and even more so in boiling water; sparingly soluble in alcohol.

Add the following:

■**Ammonium Glycyrhizate**: White or yellowish-white, hygroscopic powder. It is slightly soluble in water; very slightly soluble in anhydrous ethanol; practically insoluble in acetone. It dissolves in dilute solutions of acids and of alkali hydroxides. *NF category*: Flavors and perfumes; wetting and/or solubilizing agent. ■1S (NF31)

Ammonium Molybdate: Colorless or slightly greenish or yellowish crystals. Soluble in water; practically insoluble in alcohol.

Ammonium Phosphate: Colorless or white granules or powder, having a saline taste. Freely soluble in water; practically insoluble in acetone and in alcohol. *NF category*: Buffering agent.

Ammonium Sulfate: Colorless or white crystals or granules that decompose at temperatures above 280°. One g is soluble in about 1.5 mL of water. It is insoluble in alcohol. The pH of a 0.1 M solution is between 4.5 and 6.0.

Amobarbital Sodium: White, friable, granular powder. Is odorless, has a bitter taste, and is hygroscopic. Its solutions decompose on standing, heat accelerating the decomposition. Very soluble in water; soluble in alcohol; practically insoluble in ether and in chloroform.

Amodiaquine: Very pale yellow to light tan-yellow, odorless powder. Sparingly soluble in 1.0 N hydrochloric acid; slightly soluble in alcohol; practically insoluble in water.

Amodiaquine Hydrochloride: Yellow, crystalline powder. Is odorless and has a bitter taste. Soluble in water; sparingly soluble in alcohol; very slightly soluble in benzene, in chloroform, and in ether.

Amoxapine: White to yellowish crystalline powder. Freely soluble in chloroform; soluble in tetrahydrofuran; sparingly soluble in methanol and in toluene; slightly soluble in acetone; practically insoluble in water.

Amoxicillin: White, practically odorless, crystalline powder. Slightly soluble in water and in methanol; insoluble in benzene, in carbon tetrachloride, and in chloroform.

Amphetamine Sulfate: White, odorless, crystalline powder, having a slightly bitter taste. Its solutions are acid to litmus, having a pH of 5 to 6. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether.

Amphotericin B: Yellow to orange powder; odorless or practically so. Soluble in dimethylformamide, in dimethyl sulfoxide, and in propylene glycol; slightly soluble in methanol; insoluble in water, in anhydrous alcohol, in ether, in benzene, and in toluene.

Amphotericin B for Injection: It yields a colloidal dispersion in water.

Ampicillin: White, practically odorless, crystalline powder. Slightly soluble in water and in methanol; insoluble in benzene, in carbon tetrachloride, and in chloroform.

Ampicillin Sodium: White to off-white, odorless or practically odorless, crystalline powder. Is hygroscopic. Very soluble in water and in isotonic sodium chloride and dextrose solutions.

Amprolium ($C_{14}H_{19}ClN_4 \cdot HCl$): White to light yellow powder. Freely soluble in water, in methanol, in alcohol,

and in dimethylformamide; sparingly soluble in dehydrated alcohol; practically insoluble in isopropyl alcohol, in butyl alcohol, and in acetone.

Amyl Nitrite: Clear, yellowish liquid, having a peculiar, ethereal, fruity odor. Is volatile even at low temperatures, and is flammable. Boils at about 96°. Practically insoluble in water. Miscible with alcohol and with ether.

Amylene Hydrate: Clear, colorless liquid, having a camphoraceous odor. Its solutions are neutral to litmus. Freely soluble in water. Miscible with alcohol, with chloroform, with ether, and with glycerin. *NF category*: Solvent.

Anagrelide Hydrochloride: Off-white to pale pinkish powder. Sparingly soluble in dimethylsulfoxide and dimethylformamide; very slightly soluble in water.

Anastrozole: White to off-white crystalline powder. Very soluble in acetonitrile; freely soluble in methanol, in acetone, in alcohol, and in tetrahydrofuran.

Anethole: Colorless or faintly yellow liquid at or above 23°. Has a sweet taste and the aromatic odor of anise. Is affected by light. Freely soluble in alcohol; very slightly soluble in water. Readily miscible with ether and with chloroform. *NF category*: Flavors and perfumes.

Anileridine: White to yellowish-white, odorless to practically odorless, crystalline powder. Is oxidized on exposure to air and light, becoming darker in color. It exhibits polymorphism, and of two crystalline forms observed, one melts at about 80° and the other at about 89°. Freely soluble in alcohol and in chloroform; soluble in ether, although it may show turbidity; very slightly soluble in water.

Anileridine Hydrochloride: White or nearly white, odorless, crystalline powder. Is stable in air. Melts at about 270°, with decomposition. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in ether, and in chloroform.

Antazoline Phosphate: White to off-white, crystalline powder, having a bitter taste. Soluble in water; sparingly soluble in methanol; practically insoluble in benzene and in ether.

Anthralin: Yellowish-brown, crystalline powder. Is odorless and tasteless. Soluble in chloroform, in acetone, in benzene, and in solutions of alkali hydroxides; slightly soluble in alcohol, in ether, and in glacial acetic acid; insoluble in water.

Anticoagulant Citrate Dextrose Solution: Clear, colorless, odorless liquid. Is dextrorotatory.

Anticoagulant Citrate Phosphate Dextrose Solution: Clear, colorless to slightly yellow, odorless liquid. Is dextrorotatory.

Anticoagulant Sodium Citrate Solution: Clear and colorless liquid.

Antihemophilic Factor: White or yellowish powder. On constitution is opalescent with a slight blue tinge or is a yellowish liquid.

Cryoprecipitated Antihemophilic Factor: Yellowish, frozen solid. On thawing becomes a very viscous, yellow, gummy liquid.

Antimony Potassium Tartrate: Colorless, odorless, transparent crystals, or white powder. The crystals effloresce upon exposure to air and do not readily rehydrate even on exposure to high humidity. Its solutions are acid to litmus. Freely soluble in boiling water; soluble in water and in glycerin; insoluble in alcohol.

Antimony Sodium Tartrate: Colorless, odorless, transparent crystals, or white powder. The crystals effloresce upon exposure to air. Freely soluble in water; insoluble in alcohol.

Antipyrine: Colorless crystals, or white, crystalline powder. Is odorless and has a slightly bitter taste. Its solutions are neutral to litmus. Very soluble in water; freely soluble in alcohol and in chloroform; sparingly soluble in ether.

Antivenin (Crotalidae) Polyvalent: Solid exhibiting the characteristic structure of a freeze-dried solid; light cream in color.

Antivenin (Micrurus Fulvius): Solid exhibiting the characteristic structure of a freeze-dried solid; light cream in color.

Apomorphine Hydrochloride: Minute, white or grayish-white, glistening crystals or white powder. Is odorless. It gradually acquires a green color on exposure to light and air. Its solutions are neutral to litmus. Soluble in water at 80°; sparingly soluble in water and in alcohol; very slightly soluble in chloroform and in ether.

Apraclonidine Hydrochloride: White to off-white, odorless to practically odorless powder. Soluble in methanol; sparingly soluble in water and in alcohol; insoluble in chloroform, in ethyl acetate, and in hexanes.

Arginine: White, practically odorless crystals. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Arginine Hydrochloride: White crystals or crystalline powder, practically odorless. Freely soluble in water.

Add the following:

■**Aripiprazole:** A white to off-white, crystalline powder. Freely soluble in dichloromethane; sparingly soluble in toluene; insoluble in methanol and in water. ■^{1S} (USP36)

Aromatic Elixir: *NF* category: Vehicle (flavored and/or sweetened).

Arsanilic Acid: White to off-white, crystalline powder. Melts at about 232°. Soluble in hot water, in amyl alcohol, and in solutions of alkali carbonates; sparingly soluble in concentrated mineral acids; slightly soluble in cold water, in alcohol, and in acetic acid; insoluble in acetone, in benzene, in chloroform, in ether, and in dilute mineral acids.

Articaine Hydrochloride: White or almost white, crystalline powder. Freely soluble in water and in alcohol.

Ascorbic Acid: White or slightly yellow crystals or powder. On exposure to light it gradually darkens. In the dry state, is reasonably stable in air, but in solution rapidly oxidizes. Melts at about 190°. Freely soluble in water; sparingly soluble in alcohol; insoluble in chloroform, in ether, and in benzene. *NF* category: Antioxidant.

Ascorbyl Palmitate: White to yellowish white powder, having a characteristic odor. Soluble in alcohol; very slightly soluble in water and in vegetable oils. *NF* category: Antioxidant.

Asparagine: White crystals or a crystalline powder. Soluble in water; practically insoluble in alcohol and in ether. Its solutions are acid to litmus. It melts at about 234°.

Aspartame: White, odorless, crystalline powder, having a sweet taste. Sparingly soluble in water; slightly soluble in alcohol. Melts at about 246°. The pH of an 8 in 1000 solution is about 5. *NF* category: Sweetening agent.

Aspartame Acesulfame: White, odorless, crystalline powder. Slightly soluble in water and in ethanol. *NF* category: Sweetening agent.

Aspartic Acid: White or almost white, crystalline powder, or colorless crystals. Soluble in dilute solutions of alkali hydroxides and in dilute mineral acids; slightly soluble in water; practically insoluble in alcohol and in ether.

Aspirin: White crystals, commonly tabular or needle-like, or white, crystalline powder. Is odorless or has a faint odor. Is stable in dry air; in moist air it gradually hydrolyzes to salicylic and acetic acids. Freely soluble in alcohol; soluble in chloroform and in ether; sparingly soluble in absolute ether; slightly soluble in water.

Atenolol: White or practically white, odorless powder. Melting point 146° – 148° (crystals from ethyl acetate).

Freely soluble in methanol; sparingly soluble in alcohol; slightly soluble in water and in isopropanol.

Add the following:

■**Atomoxetine Hydrochloride:** White to practically white solid. Sparingly soluble in water. ■^{1S} (USP36)

Atorvastatin Calcium: White to off-white crystalline powder. Freely soluble in methanol; slightly soluble in alcohol; very slightly soluble in distilled water, in pH 7.4 phosphate buffer, and in acetonitrile; insoluble in aqueous solutions of pH 4 and below.

Atovaquone: Yellow powder. Freely soluble in *N*-methyl-2-pyrrolidone and in tetrahydrofuran; soluble in chloroform; sparingly soluble in acetone, in di-*n*-butyl adipate, in dimethyl sulfoxide, and in polyethylene glycol 400; slightly soluble in alcohol, in 1,3-butanediol, in ethyl acetate, in glycerin, in octanol, and in polyethylene glycol 200; very slightly soluble in 0.1 N sodium hydroxide; insoluble in water.

Atracurium Besylate: White to yellowish-white powder, slightly hygroscopic. Very soluble in acetonitrile, in alcohol, and in methylene chloride; soluble in water.

Atropine: White crystals, usually needle-like, or white, crystalline powder. Its saturated solution is alkaline to phenolphthalein TS. Is optically inactive, but usually contains some levorotatory hyoscyamine. Freely soluble in alcohol and in chloroform; soluble in glycerin and in ether; slightly soluble in water; sparingly soluble in water at 80°.

Atropine Sulfate: Colorless crystals, or white, crystalline powder. Odorless; effloresces in dry air; is slowly affected by light. Very soluble in water; freely soluble in alcohol and even more so in boiling alcohol; freely soluble in glycerin.

Activated Attapulgate: Cream-colored, micronized, nonswelling powder, free from gritty particles. The high heat treatment used in its preparation causes it to yield only moderately viscous aqueous suspensions, its dispersion consisting mainly of particle groups. Insoluble in water. *NF* category: Suspending and/or viscosity-increasing agent.

Colloidal Activated Attapulgate: Cream-colored, micronized, nonswelling powder, free from gritty particles. Yields viscous aqueous suspensions, as a result of dispersion into its constituent ultimate particles. Insoluble in water. *NF* category: Suspending and/or viscosity-increasing agent.

Aurothioglucose: Yellow, odorless or practically odorless powder. Is stable in air. An aqueous solution is unstable on long standing. The pH of its 1 in 100 solution is about 6.3. Freely soluble in water; practically insoluble in acetone, in alcohol, in chloroform, and in ether.

Azatadine Maleate: White to light cream-colored, odorless powder. Melts at about 153°. Freely soluble in water, in alcohol, in chloroform, and in methanol; practically insoluble in benzene and in ether.

Azathioprine: Pale yellow, odorless powder. Soluble in dilute solutions of alkali hydroxides; sparingly soluble in dilute mineral acids; very slightly soluble in alcohol and in chloroform; insoluble in water.

Azathioprine Sodium for Injection: Bright yellow, hygroscopic, amorphous mass or cake.

Azithromycin: White or almost white powder. Freely soluble in anhydrous ethanol and in methylene chloride; practically insoluble in water.

Aztreonam: White, odorless, crystalline powder. Soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methanol; very slightly soluble in dehydrated alcohol; practically insoluble in ethyl acetate, in chloroform, and in toluene.

Bacampicillin Hydrochloride: White or practically white powder. Is hygroscopic. Freely soluble in alcohol and in chloroform; soluble in methylene chloride and in water; very slightly soluble in ether.

Bacitracin: White to pale buff powder, odorless or having a slight odor. Is hygroscopic. Its solutions deteriorate rapidly at room temperature. Is precipitated from its solutions and is inactivated by salts of many of the heavy metals. Freely soluble in water; soluble in alcohol, in methanol, and in glacial acetic acid, the solution in the organic solvents usually showing some insoluble residue; insoluble in acetone, in chloroform, and in ether.

Bacitracin Zinc: White to pale tan powder, odorless or having a slight odor. Is hygroscopic. Sparingly soluble in water.

Baclofen: White to off-white, crystalline powder. Is odorless or practically so. Slightly soluble in water; very slightly soluble in methanol; insoluble in chloroform.

Balsalazide Disodium: Orange to yellow powder. Freely soluble in water and in isotonic saline; sparingly soluble in methanol and in alcohol; practically insoluble in all other organic solvents.

Adhesive Bandage: The compress of Adhesive Bandage is substantially free from loose threads or ravelings. The adhesive strip may be perforated, and the back may be coated with a water-repellent film.

Gauze Bandage: One continuous piece, tightly rolled, in various widths and lengths and substantially free from loose threads and ravelings.

Barium Hydroxide Lime: White or grayish-white granules. May have a color if an indicator has been added. *NF category:* Sorbent, carbon dioxide.

Barium Sulfate: Fine, white, odorless, tasteless, bulky powder, free from grittiness. Practically insoluble in water, in organic solvents, and in solutions of acids and of alkalis.

Barium Sulfate for Suspension: White or colored, bulky or granular powder.

BCG Vaccine: White to creamy white, dried mass, having the characteristic texture of material dried in the frozen state.

Beclomethasone Dipropionate: White to cream white, odorless powder. Very soluble in chloroform; freely soluble in acetone and in alcohol; very slightly soluble in water.

Behenoyl Polyoxylglycerides: Waxy solid or fine powder. Soluble in methylene chloride; insoluble in alcohol; dispersible in water. *NF category:* Tablet and/or capsule lubricant.

Belladonna Leaf: When moistened, its odor is slight, somewhat tobacco-like. Its taste is somewhat bitter and acrid.

Benazepril Hydrochloride: White to off-white, crystalline powder. Soluble in water, in methanol, and in alcohol.

Bendroflumethiazide: White to cream-colored, finely divided, crystalline powder. Is odorless, or has a slight odor. Melts at about 220°. Freely soluble in alcohol and in acetone; practically insoluble in water.

Benoxinate Hydrochloride: White, or slightly off-white, crystals or crystalline powder. Is odorless, or has a slight characteristic odor, has a salty taste, and exhibits local anesthetic properties when placed upon the tongue. Its solutions are neutral to litmus, and it melts at about 158°. Very soluble in water; freely soluble in chloroform and in alcohol; insoluble in ether.

Bentonite: Very fine, odorless, pale buff or cream-colored to grayish powder, free from grit. Has a slightly earthy taste. Is hygroscopic. Insoluble in water, but swells to approximately twelve times its volume when added to water; insoluble in, and does not swell in, organic solvents. *NF category:* Suspending and/or viscosity-increasing agent.

Purified Bentonite: Odorless, tasteless, fine (micronized) powder or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerin. *NF category:* Suspending and/or viscosity-increasing agent.

Bentonite Magma: *NF category:* Suspending and/or viscosity-increasing agent.

Change to read:

Benzaldehyde: Colorless, strongly refractive liquid. ▲^{NF31} Is affected by light. Slightly soluble in water. Miscible with alcohol, with ether, and with fixed and volatile oils. ▲The specific gravity is 1.041–1.046 at 25° (see *Specific Gravity* (841)), and the refractive index is 1.544–1.546 at 20° (see *Refractive Index* (831)). ▲^{NF31} *NF category:* Flavors and perfumes.

Benzaldehyde Elixir, Compound: *NF category:* Flavored and/or sweetened vehicle.

Benzalkonium Chloride: White or yellowish-white, thick gel or gelatinous pieces. Usually has a mild, aromatic odor. Its aqueous solution has a bitter taste, foams strongly when shaken, and usually is slightly alkaline. Very soluble in water and in alcohol. Anhydrous form freely soluble in benzene, and slightly soluble in ether. *NF category:* Antimicrobial preservative; wetting and/or solubilizing agent.

Benzalkonium Chloride Solution: Clear liquid; colorless or slightly yellow unless a color has been added. Has an aromatic odor and a bitter taste. *NF category:* Antimicrobial preservative.

Benzethonium Chloride: White crystals, having a mild odor. Its solution (1 in 100) is slightly alkaline to litmus. Soluble in water, in alcohol, and in chloroform; slightly soluble in ether. *NF category:* Antimicrobial preservative; wetting and/or solubilizing agent.

Benzethonium Chloride Solution: Odorless, clear liquid, slightly alkaline to litmus.

Benzethonium Chloride Tincture: Clear liquid, having the characteristic odor of acetone and of alcohol.

Benzocaine: Small, white crystals or white, crystalline powder. Is odorless, is stable in air, and exhibits local anesthetic properties when placed upon the tongue. Freely soluble in alcohol, in chloroform, and in ether; sparingly soluble in almond oil and in olive oil; very slightly soluble in water. Dissolves in dilute acids.

Benzoic Acid: White crystals, scales, or needles. Has a slight odor, usually suggesting benzaldehyde or benzoin. Somewhat volatile at moderately warm temperatures. Freely volatile in steam. Freely soluble in alcohol, in chloroform, and in ether; slightly soluble in water. *NF category:* Antimicrobial preservative.

Benzoin: Sumatra Benzoin has an aromatic and balsamic odor. When heated it does not emit a pinaceous odor. When Sumatra Benzoin is digested with boiling water, the odor suggests cinnamates or storax. Its taste is aromatic and slightly acid. Siam Benzoin has an agreeable, balsamic, vanilla-like odor. Its taste is aromatic and slightly acid.

Benzonate: Clear, pale yellow, viscous liquid, having a faint, characteristic odor. Has a bitter taste, and exhibits local anesthetic properties when placed upon the tongue. Miscible with water in all proportions. Freely soluble in chloroform, in alcohol, and in benzene.

Hydrous Benzoyl Peroxide: White, granular powder, having a characteristic odor. Soluble in acetone, in chloroform, and in ether; sparingly soluble in water and in alcohol.

Benzoyl Peroxide Gel: A soft, white gel, having a characteristic odor.

Benzoyl Peroxide Lotion: White, viscous, creamy lotion, having a characteristic odor.

Benzotropine Mesylate: White, slightly hygroscopic, crystalline powder. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether.

Benzyl Alcohol: Clear, colorless, oily liquid. Boils at about 206°, without decomposition. Is neutral to litmus.

Freely soluble in 50% alcohol; sparingly soluble in water. Miscible with alcohol, with ether, and with chloroform. The specific gravity is between 1.042 and 1.047. *NF category:* Antimicrobial preservative.

Benzyl Benzoate: Clear, colorless, oily liquid having a slight aromatic odor and producing a sharp, burning sensation on the tongue. Practically insoluble in water and in glycerin. Miscible with alcohol, with ether, and with chloroform. *NF category:* Solvent.

Beta Carotene: Red or reddish-brown to violet-brown crystals or crystalline powder. Soluble in carbon disulfide, in benzene, and in chloroform; sparingly soluble in ether, in solvent hexane, and in vegetable oils; practically insoluble in methanol and in alcohol; insoluble in water and in acids and in alkalies.

Betadex: White, practically odorless, fine crystalline powder having a slightly sweet taste. Sparingly soluble in water. *NF category:* Sequestering agent.

Betadex Sulfolbutyl Ether Sodium: White to off-white, amorphous powder. Freely soluble in water; sparingly soluble in methanol; practically insoluble in ethanol, in *n*-hexane, in 1-butanol, in acetonitrile, in 2-propanol, and in ethyl acetate. *NF category:* Complexing agent; sequestering agent; wetting and/or solubilizing agent.

Betahistine Hydrochloride: White to almost yellow, crystalline powder. Very hygroscopic. Melts between 151° and 154°. Very soluble in water; freely soluble in alcohol; practically insoluble in isopropyl alcohol.

Betaine Hydrochloride: White, crystalline powder. Soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Betamethasone: White to practically white, odorless, crystalline powder. Melts at about 240°, with some decomposition. Sparingly soluble in acetone, in alcohol, in dioxane, and in methanol; very slightly soluble in chloroform and in ether; insoluble in water.

Betamethasone Acetate: White to creamy white, odorless powder. Sinters and resolidifies at about 165°, and remelts at about 200° or 220°, with decomposition (see *Melting Range or Temperature* (741)). Freely soluble in acetone; soluble in alcohol and in chloroform; practically insoluble in water.

Betamethasone Benzoate: White to practically white, practically odorless powder. Melts at about 220°, with decomposition. Soluble in alcohol, in methanol, and in chloroform; insoluble in water.

Betamethasone Dipropionate: White to cream-white, odorless powder. Freely soluble in acetone and in chloroform; sparingly soluble in alcohol; insoluble in water.

Betamethasone Sodium Phosphate: White to practically white, odorless powder. Is hygroscopic. Freely soluble in water and in methanol; practically insoluble in acetone and in chloroform.

Betamethasone Valerate: White to practically white, odorless powder. Melts at about 190°, with decomposition. Freely soluble in acetone and in chloroform; soluble in alcohol; slightly soluble in benzene and in ether; practically insoluble in water.

Betaxolol Hydrochloride: White, crystalline powder. Freely soluble in water, in alcohol, in chloroform, and in methanol.

Bethanechol Chloride: Colorless or white crystals or white, crystalline powder, usually having a slight, amine-like odor. Is hygroscopic. Exhibits polymorphism, and of two crystalline forms observed, one melts at about 211° and the other melts at about 219°. Freely soluble in water and in alcohol; insoluble in chloroform and in ether.

Bicalutamide: Fine, white to off-white powder. Freely soluble in tetrahydrofuran and in acetone; soluble in acetonitrile; sparingly soluble in methanol; slightly soluble in alcohol.

Biotin: Practically white, crystalline powder. Very slightly soluble in water and in alcohol; insoluble in other common organic solvents.

Biperiden: White, practically odorless, crystalline powder. Freely soluble in chloroform; sparingly soluble in alcohol; practically insoluble in water.

Biperiden Hydrochloride: White, practically odorless, crystalline powder. Melts at about 275°, with decomposition. Is optically inactive. Sparingly soluble in methanol; slightly soluble in water, in ether, in alcohol, and in chloroform.

Bisacodyl: White to off-white, crystalline powder, in which the number of particles having a longest diameter smaller than 50 µm predominate. Soluble in chloroform and in benzene; sparingly soluble in alcohol and in methanol; slightly soluble in ether; practically insoluble in water.

Milk of Bismuth: Thick, white, opaque suspension that separates on standing. Is odorless and practically tasteless. Miscible with water and with alcohol.

Bismuth Citrate: White, amorphous or crystalline powder. Stable in air. Melts at about 300°, with decomposition. Soluble in ammonia TS and in solutions of alkali citrates; insoluble in water and in alcohol.

Bismuth Subcarbonate: White or almost white powder. Practically insoluble in water, in alcohol, and in ether. Dissolves in dilute acids with effervescence.

Bismuth Subgallate: Amorphous, bright yellow powder. Is odorless and tasteless. Is stable in air, but is affected by light. Dissolves readily with decomposition in warm, moderately dilute hydrochloric, nitric, or sulfuric acid; readily dissolved by solutions of alkali hydroxides, forming a clear, yellow liquid that rapidly assumes a deep red color. Practically insoluble in water, in alcohol, in chloroform, and in ether; insoluble in very dilute mineral acids.

Bismuth Subnitrate: White, slightly hygroscopic powder. Practically insoluble in water and in alcohol; readily dissolved by hydrochloric acid or by nitric acid.

Bismuth Subsalicylate: Fine to off-white, microcrystalline, odorless, tasteless powder. Practically insoluble in water, in alcohol, and in ether. Reacts with alkalies and mineral acids.

Bisoprolol Fumarate: White, crystalline powder. Very soluble in water and in methanol; freely soluble in chloroform, in glacial acetic acid, and in alcohol; slightly soluble in acetone and in ethyl acetate.

Bleomycin Sulfate: Cream-colored, amorphous powder. Very soluble in water.

Anti-A Blood Grouping Serum: Liquid Serum is a clear or slightly opalescent fluid unless artificially colored blue. Dried Serum is light yellow to deep cream color, unless artificially colored as indicated for liquid Serum. The liquid Serum may develop slight turbidity on storage. The dried Serum may show slight turbidity upon reconstitution for use.

Anti-B Blood Grouping Serum: Liquid Serum is a clear or slightly opalescent fluid unless artificially colored yellow. Dried Serum is light yellow to deep cream color, unless artificially colored as indicated for liquid Serum. The liquid Serum may develop a slight turbidity on storage. The dried Serum may show slight turbidity upon reconstitution for use.

Blood Grouping Serums Anti-D, Anti-C, Anti-E, Anti-c, Anti-e: The liquid Serums are clear, slightly yellowish fluids, that may develop slight turbidity on storage. The dried Serums are light yellow to deep cream color.

Blood Group Specific Substances A, B, and AB: Clear solution that may have a slight odor because of the preservative.

Red Blood Cells: Dark red in color when packed. May show a slight creamy layer on the surface and a small supernatant layer of yellow or opalescent plasma. Also supplied in

deep-frozen form with added cryophylactic substance to extend storage time.

Whole Blood: Deep red, opaque liquid from which the corpuscles readily settle upon standing for 24 to 48 hours, leaving a clear, yellowish or pinkish supernatant layer of plasma.

Boric Acid: Colorless, odorless scales of a somewhat pearly luster, or crystals, or white powder that is slightly unctuous to the touch. Is stable in air. Freely soluble in glycerin, in boiling water, and in boiling alcohol; soluble in water and in alcohol. *NF category:* Buffering agent.

Botulism Antitoxin: Transparent or slightly opalescent liquid, practically colorless, and practically odorless or having an odor because of the antimicrobial agent.

Bretylum Tosylate: White, crystalline powder. Is hygroscopic. Freely soluble in water, in methanol, and in alcohol; practically insoluble in ether, in ethyl acetate, and in hexane.

Brinzolamide: White or almost white powder. Slightly soluble in alcohol and in methanol; insoluble in water.

Bromocriptine Mesylate: White or slightly colored, fine crystalline powder, odorless or having a weak, characteristic odor.

Bromodiphenhydramine Hydrochloride: White to pale buff, crystalline powder, having no more than a faint odor. Freely soluble in water and in alcohol; soluble in isopropyl alcohol; insoluble in ether and in solvent hexane.

Brompheniramine Maleate: White, odorless, crystalline powder. Freely soluble in water; soluble in alcohol and in chloroform; slightly soluble in ether and in benzene.

Budesonide: White to off-white, odorless, crystalline powder. Freely soluble in chloroform; sparingly soluble in alcohol; practically insoluble in water and in heptane.

Bumetanide: Practically white powder. Soluble in alkaline solutions; slightly soluble in water.

Bupivacaine Hydrochloride: White, odorless, crystalline powder. Melts at about 248°, with decomposition. Freely soluble in water and in alcohol; slightly soluble in chloroform and in acetone.

Bupivacaine Hydrochloride Injection: Clear, colorless solution.

Bupivacaine Hydrochloride and Epinephrine Injection: Clear, colorless solution.

Bupropion Hydrochloride: White powder. Soluble in water, in 0.1 N hydrochloric acid, and in alcohol.

Busulfan: White, crystalline powder. Sparingly soluble in acetone; slightly soluble in alcohol; very slightly soluble in water.

Buspiron Hydrochloride: White crystalline powder. Very soluble in water; freely soluble in methanol and in methylene chloride; sparingly soluble in ethanol and in acetonitrile; very slightly soluble in ethyl acetate; practically insoluble in hexanes.

Butabarbital: White, odorless, crystalline powder. Soluble in alcohol, in chloroform, in ether, and in solutions of alkali hydroxides and carbonates; very slightly soluble in water.

Butabarbital Sodium: White powder, having a bitter taste. Freely soluble in water and in alcohol; practically insoluble in absolute ether.

Butalbital: White, crystalline, odorless powder, having a slightly bitter taste. Is stable in air. Its saturated solution is acid to litmus. Freely soluble in alcohol, in ether, and in chloroform; soluble in boiling water, and in solutions of fixed alkalis and alkali carbonates; slightly soluble in cold water.

Butamben: White, crystalline powder. Is odorless and tasteless. Soluble in dilute acids, in alcohol, in chloroform, in ether, and in fixed oils; very slightly soluble in water. Is slowly hydrolyzed when boiled with water.

Butane: Colorless, flammable gas (boiling temperature is about -0.5°). One volume of water dissolves 0.15 volume, and 1 volume of alcohol dissolves 18 volumes at 17° and 770 mm; 1 volume of ether or chloroform at 17° dissolves 25 or 30 volumes, respectively. Vapor pressure at 21° is about 1620 mm of mercury (17 psig). *NF category:* Aerosol propellant.

Butoconazole Nitrate: White to off-white, crystalline powder. Melts at about 160° . Sparingly soluble in methanol; slightly soluble in acetonitrile, in acetone, in dichloromethane, and in tetrahydrofuran; very slightly soluble in ethyl acetate; practically insoluble in water.

Butorphanol Tartrate: White powder. Its solutions are slightly acidic. Melts between 217° and 219° , with decomposition. Soluble in dilute acids; sparingly soluble in water; slightly soluble in methanol; insoluble in alcohol, in chloroform, in ethyl acetate, in ethyl ether, and in hexane.

Butyl Alcohol: Clear, colorless, mobile liquid, having a characteristic, penetrating vinous odor. Soluble in water. Miscible with alcohol, with ether, and with many other organic solvents. *NF category:* Solvent.

Add the following:

■Butyl Palmitostearate: Colorless or pale yellowish waxy solid at temperatures below 17° – 24° or colorless or pale yellowish liquid at temperatures of 17° – 24° or above. Soluble in acetone, in alcohol, in ether, in mineral oils, and in vegetable oils; practically insoluble in water and in propylene glycol. *NF category:* Emulsifying and/or solubilizing agent; flavors and perfumes; plasticizer. ■1S (NF31)

Add the following:

■Butyl Stearate: Colorless or pale yellowish waxy solid at temperatures below 19° – 24° or colorless or pale yellowish liquid at temperatures of 19° – 24° or above. Soluble in acetone, in alcohol, in ether, in mineral oils, and in vegetable oils; practically insoluble in water and in propylene glycol. *NF category:* Emulsifying and/or solubilizing agent; flavors and perfumes; plasticizer. ■1S (NF31)

Butylated Hydroxyanisole: White or slightly yellow, waxy solid, having a faint, characteristic odor. Freely soluble in alcohol, in propylene glycol, in chloroform, and in ether; insoluble in water. *NF category:* Antioxidant.

Butylated Hydroxytoluene: White, crystalline solid, having a faint, characteristic odor. Freely soluble in alcohol, in chloroform, and in ether; insoluble in water and in propylene glycol. *NF category:* Antioxidant.

Butylparaben: Small, colorless crystals or white powder. Freely soluble in acetone, in alcohol, in ether, and in propylene glycol; very slightly soluble in water and in glycerin. *NF category:* Antimicrobial preservative.

Cabergoline: White or almost white, crystalline powder. Freely soluble in alcohol (96%); slightly soluble in 0.1 M hydrochloric acid; very slightly soluble in hexane; practically insoluble in water.

Caffeine: White powder or white, glistening needles, usually matted together. Is odorless and has a bitter taste. Its solutions are neutral to litmus. The hydrate is efflorescent in air. Freely soluble in chloroform; sparingly soluble in water and in alcohol; slightly soluble in ether.

Calamine: Pink, odorless, practically tasteless, fine powder. Soluble in mineral acids; insoluble in water.

Calcitriol: White or almost white crystals. Freely soluble in alcohol; soluble in ether and in fatty oils; practically insoluble in water. It is sensitive to air, heat, and light.

Calcium Acetate: White, odorless or almost odorless, hygroscopic, crystalline powder. When heated to above 160° , it decomposes to calcium carbonate and acetone.

Freely soluble in water; slightly soluble in methanol; practically insoluble in acetone, in dehydrated alcohol, and in benzene.

Calcium Ascorbate: White to slightly yellow, practically odorless powder. Freely soluble in water (approximately 50 g per 100 mL); slightly soluble in alcohol; insoluble in ether.

Calcium Carbonate: Fine, white, odorless, tasteless, microcrystalline powder. Is stable in air. Practically insoluble in water. Its solubility in water is increased by the presence of any ammonium salt or of carbon dioxide. The presence of any alkali hydroxide reduces its solubility. Insoluble in alcohol. Dissolves with effervescence in 1 N acetic acid, in 3 N hydrochloric acid, and in 2 N nitric acid. *NF category:* Tablet and/or capsule diluent.

Calcium Chloride: White, hard, odorless fragments or granules. Is deliquescent. Very soluble in boiling water; freely soluble in water, in alcohol, and in boiling alcohol. *NF category:* Desiccant.

Calcium Citrate: White, odorless, crystalline powder. Freely soluble in diluted 3 N hydrochloric acid and in diluted 2 N nitric acid; slightly soluble in water; insoluble in alcohol.

Calcium Gluceptate: White to faintly yellow, amorphous powder. Is stable in air, but the hydrous forms may lose part of their water of hydration on standing. Freely soluble in water; insoluble in alcohol and in many other organic solvents.

Calcium Gluconate: White, crystalline, odorless, tasteless granules or powder. Is stable in air. Its solutions are neutral to litmus. Freely soluble in boiling water; sparingly (and slowly) soluble in water; insoluble in alcohol.

Calcium Hydroxide: White powder. Has an alkaline, slightly bitter taste. Soluble in glycerin and in syrup; slightly soluble in water; very slightly soluble in boiling water; insoluble in alcohol.

Calcium Hydroxide Solution: Clear, colorless liquid having an alkaline taste. Is alkaline to litmus.

Calcium Lactate: White, practically odorless granules or powder. The pentahydrate is somewhat efflorescent and at 120° becomes anhydrous. The pentahydrate is soluble in water; it is practically insoluble in alcohol.

Calcium Levulinate: White, crystalline or amorphous, powder, having a faint odor suggestive of burnt sugar. Has a bitter, salty taste. Freely soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform.

Calcium Pantothenate: Slightly hygroscopic, white powder. Is odorless and has a bitter taste. Freely soluble in water; soluble in glycerin; practically insoluble in alcohol, in chloroform, and in ether.

Racemic Calcium Pantothenate: White, slightly hygroscopic powder, having a faint, characteristic odor, and a bitter taste. Is stable in air. Its solutions are neutral or alkaline to litmus. Is optically inactive. Freely soluble in water; soluble in glycerin; practically insoluble in alcohol, in chloroform, and in ether.

Dibasic Calcium Phosphate: White, odorless, tasteless powder. Is stable in air. Soluble in 3 N hydrochloric acid and in 2 N nitric acid; practically insoluble in water; insoluble in alcohol. *NF category:* Tablet and/or capsule diluent.

Tribasic Calcium Phosphate: White, odorless, tasteless powder. Is stable in air. Freely soluble in 3 N hydrochloric acid and in 2 N nitric acid; practically insoluble in water; insoluble in alcohol. *NF category:* Tablet and/or capsule diluent.

Calcium Polycarbophil: White to creamy white powder. Insoluble in water, in dilute acids, in dilute alkalies, and in common organic solvents.

Calcium Propionate: Occurs as a white crystalline solid. One g dissolves in about 3 mL of water. *NF category:* Antimicrobial preservative.

Calcium Saccharate: White, odorless, tasteless, crystalline powder. Soluble in dilute mineral acids and in solutions of calcium gluconate; slightly soluble in boiling water; very slightly soluble in alcohol, and in cold water; practically insoluble in ether and in chloroform.

Calcium Silicate: White to off-white, free-flowing powder that remains so after absorbing relatively large amounts of water or other liquids. Insoluble in water. Forms a gel with mineral acids. *NF category:* Glidant and/or anticaking agent.

Calcium Stearate: Fine, white to yellowish-white, bulky powder having a slight, characteristic odor. Is unctuous, and is free from grittiness. Insoluble in water, in alcohol, and in ether. *NF category:* Tablet and/or capsule lubricant.

Calcium Sulfate: Fine, white to slightly yellow-white, odorless powder. Soluble in 3 N hydrochloric acid; slightly soluble in water. *NF category:* Desiccant; tablet and/or capsule diluent.

Calcium Undecylenate: Fine, white powder, having a characteristic odor and no grit. Slightly soluble in hot alcohol; practically insoluble in water, in ether, in chloroform, in acetone, and in cold alcohol.

Camphor: Colorless or white crystals, granules, or crystalline masses; or colorless to white, translucent, tough masses. Has a penetrating, characteristic odor and a pungent, aromatic taste. Specific gravity is about 0.99. Slowly volatilizes at ordinary temperatures. Slightly soluble in water; very soluble in alcohol, in chloroform, and in ether; freely soluble in carbon disulfide, in solvent hexane, and in fixed and volatile oils.

Candelilla Wax: A hard, yellowish-brown-opaque to translucent wax. Its specific gravity is about 0.983. Soluble in chloroform and in toluene; insoluble in water.

Candesartan Cilexetil: White to off-white powder. Sparingly soluble in methanol; practically insoluble in water.

Canola Oil: Clear, pale yellow, slightly viscous liquid. Practically insoluble in water and in alcohol. Miscible with light petroleum (bp: 40° to 60°). *NF category:* Solvent; vehicle (oleaginous).

Capecitabine: White to off-white crystalline powder. Freely soluble in methanol; soluble in acetonitrile and in alcohol; sparingly soluble in water.

Capreomycin Sulfate: White to practically white, amorphous powder. Freely soluble in water; practically insoluble in most organic solvents.

Add the following:

▲**Caprylic Acid:** Clear, colorless or slightly yellowish, oily liquid. Very soluble in acetone and in alcohol; very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides. *NF category:* Emulsifying and/or solubilizing agent.

▲*NF31*

Caprylocaproyl Polyoxylglycerides: Pale yellow, oily liquids. Dispersible in hot water; freely soluble in methylene chloride. *NF category:* Ointment base; solvent.

Capsaicin: Off-white powder. Melts at about 65°. Soluble in alcohol, in benzene, in chloroform; slightly soluble in carbon disulfide; practically insoluble in cold water.

Capsicum Oleoresin: Dark red, oily liquid. Soluble in alcohol, in acetone, in ether, in chloroform, and in volatile oils; soluble with opalescence in fixed oils.

Captopril: White to off-white, crystalline powder, which may have a characteristic, sulfide-like odor. Melts in the range of 104° to 110°. Freely soluble in water, in methanol, in alcohol, and in chloroform.

Caramel: Thick, dark brown liquid having the characteristic odor of burnt sugar, and a pleasant, bitter taste. One part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish-orange color. The color of this

solution is not changed and no precipitate is formed after exposure to sunlight for 6 hours. When spread in a thin layer on a glass plate, it appears homogeneous, reddish-brown, and transparent. Miscible with water. Soluble in dilute alcohol up to 55% (v/v). Immiscible with ether, with chloroform, with acetone, with benzene, and with solvent hexane. *NF category*: Color.

Carbachol: White powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether.

Carbamazepine: White to off-white powder. Soluble in alcohol and in acetone; practically insoluble in water.

Carbamide Peroxide Topical Solution: Clear, colorless, viscous liquid, having a characteristic odor and taste.

Carbenicillin Disodium: White to off-white, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether.

Carbenicillin Indanyl Sodium: White to off-white powder. Soluble in water and in alcohol.

Carbidopa: White to creamy white, odorless or practically odorless, powder. Freely soluble in 3 N hydrochloric acid; slightly soluble in water, and in methanol; practically insoluble in alcohol, in acetone, in chloroform, and in ether.

Carbinoxamine Maleate: White, odorless, crystalline powder. Very soluble in water; freely soluble in alcohol and in chloroform; very slightly soluble in ether.

Carbol-Fuchsin Topical Solution: Dark purple liquid, which appears purplish red when spread in a thin film.

Carbomer 910: White, fluffy powder, having a slight, characteristic odor. Is hygroscopic. The pH of a 1 in 100 dispersion is about 3. When neutralized with alkali hydroxides or with amines, it dissolves in water, in alcohol, and in glycerin. *NF category*: Suspending and/or viscosity-increasing agent.

Carbomer 934: See *Carbomer 910*.

Carbomer 934P: See *Carbomer 910*.

Carbomer 940: See *Carbomer 910*.

Carbomer 941: See *Carbomer 910*.

Carbomer 1342: See *Carbomer 910*.

Change to read:

Carbomer Copolymer: White, hygroscopic powder. It swells in water when a dispersion of it is neutralized with sodium hydroxide to a pH within the range of 7.3 to 7.8. (ERR 1-May-2012) *NF category*: Emulsifying and/or solubilizing agent; suspending and/or viscosity increasing agent; tablet binder.

Carbomer Homopolymer: White, fluffy hygroscopic powder, having a slight, characteristic odor. The pH of a 1 in 100 dispersion in water is about 3. When neutralized with alkali hydroxides or with amines, it swells giving the appearance of dissolving in water; when neutralized with lower amines and alkanolamines, it swells giving the appearance of dissolving in methanol or glycerin; when neutralized with ethoxylated long-chain (C_{14} – C_{18}) amines, it swells giving the appearance of dissolving in ethanol. *NF category*: Tablet binder; suspending and/or viscosity-increasing agent.

Carbomer Interpolymer: White, hygroscopic powder. It swells in water when a dispersion of it is neutralized with sodium hydroxide to a pH within the range of 5.5 to 9. *NF category*: Emulsifying and/or solubilizing agent; suspending and/or viscosity increasing agent; tablet binder.

Carbon Dioxide: Odorless, colorless gas. Its solutions are acid to litmus. One L at 0° and at a pressure of 760 mm of mercury weighs 1.977 g. One volume dissolves in about 1 volume of water. *NF category*: Air displacement.

Carboprost Tromethamine: White to off-white powder. Soluble in water.

Carboxymethylcellulose Calcium: White to yellowish-white powder. Is hygroscopic. Practically insoluble in alcohol, in acetone, in ether, in chloroform, and in benzene. It swells with water to form a suspension; the pH of the suspension, obtained by shaking 1 g with 100 mL of water, is between 4.5 and 6.0. *NF category*: Suspending and/or viscosity-increasing agent.

Carboxymethylcellulose Sodium: White to cream-colored powder or granules. The powder is hygroscopic. Is easily dispersed in water to form colloidal solutions. Insoluble in alcohol, in ether, and in most other organic solvents. *NF category*: Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Carboxymethylcellulose Sodium 12: Colorless or white to off-white powder or granules. Is odorless. Water solubility depends on degree of substitution (easily dispersed in water at all temperatures, forming a clear, colloidal solution). Insoluble in acetone, in alcohol, in ether, and in toluene. *NF category*: Suspending and/or viscosity-increasing agent.

Enzymatically-Hydrolyzed Carboxymethylcellulose Sodium: White or slightly yellowish or grayish, odorless, slightly hygroscopic granular or fibrous powder. Soluble in water; insoluble in alcohol. *NF category*: Coating agent; suspending and/or viscosity-increasing agent.

Low-Substituted Carboxymethylcellulose Sodium: A white or almost white powder or short fibers. Practically insoluble in acetone, in alcohol, and in toluene. It swells in water to form a gel.

Carisoprodol: White, crystalline powder, having a mild, characteristic odor and a bitter taste. Freely soluble in alcohol, in chloroform, and in acetone; very slightly soluble in water.

Carmellose: White powder. Practically insoluble in ethanol (99.5%). Swells with water to form a suspension. Becomes viscous in sodium hydroxide TS. Is hygroscopic. *NF category*: Suspending and/or viscosity increasing agent.

Carmustine: Light yellow powder. Freely soluble in ether.

Carprofen: White crystalline powder. Freely soluble in ether, in acetone, in ethyl acetate, and in sodium hydroxide TS or sodium carbonate TS; practically insoluble in water.

Carrageenan: Yellowish or tan to white, coarse to fine powder. Is practically odorless and has a mucilaginous taste. Soluble in water at a temperature of about 80°, forming a viscous, clear or slightly opalescent solution that flows readily. Disperses in water more readily if first moistened with alcohol, with glycerin, or with a saturated solution of sucrose in water. *NF category*: Suspending and/or viscosity-increasing agent.

Carvedilol: White or nearly white, crystalline powder. Slightly soluble in alcohol; practically insoluble in water and in dilute acids.

Casanthranol: Light tan to brown, amorphous, hygroscopic powder. Freely soluble in water, with some residue; partially soluble in methanol and in hot isopropyl alcohol; practically insoluble in acetone.

Cascara Sagrada: Has a distinct odor and a bitter and slightly acid taste.

Castor Oil: Pale yellowish or almost colorless, transparent, viscid liquid. Has a faint, mild odor; is free from foreign and rancid odor; and has a bland, characteristic taste. Soluble in alcohol. Miscible with dehydrated alcohol, with glacial acetic acid, with chloroform, and with ether. *NF category*: Plasticizer.

Hydrogenated Castor Oil: White, crystalline wax. Insoluble in water and in most common organic solvents. *NF category*: Stiffening agent.

Cefaclor: White to off-white, crystalline powder. Slightly soluble in water; practically insoluble in methanol, in chloroform, and in benzene.

Cefadroxil: White to off-white, crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether.

Cefamandole Nafate: White, odorless, crystalline solid. Soluble in water and in methanol; practically insoluble in ether, in chloroform, in benzene, and in cyclohexane.

Cefazolin: White to slightly off-white, odorless, crystalline powder. Melts at about 198° to 200°, with decomposition. Soluble in dimethylformamide and in pyridine; sparingly soluble in acetone; slightly soluble in alcohol, in methanol, and in water; very slightly soluble in ethyl acetate, in isopropyl alcohol, and in methyl isobutyl ketone; practically insoluble in benzene, in chloroform, in ether, and in methylene chloride.

Cefazolin Sodium: White to off-white, practically odorless, crystalline powder, or white to off-white solid. Freely soluble in water, in saline TS, and in dextrose solutions; very slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Cefdinir: White to light-yellow crystalline powder. Sparingly soluble in 0.1 M phosphate buffer (pH 7) solution; practically insoluble in water, in alcohol, and in diethyl ether.

Cefepime Hydrochloride: White to off-white, crystalline, nonhygroscopic solid. Freely soluble in water.

Cefepime for Injection: White to pale yellow powder. Freely soluble in water.

Cefixime: White to light yellow, crystalline powder. Soluble in methanol and in propylene glycol; slightly soluble in alcohol, in acetone, and in glycerin; very slightly soluble in 70% sorbitol and in octanol; practically insoluble in ether, in ethyl acetate, in hexane, and in water.

Cefmenoxime Hydrochloride: White to light orange-yellow crystals or crystalline powder. Freely soluble in formamide; slightly soluble in methanol; very slightly soluble in water; practically insoluble in dehydrated alcohol and in ether.

Cefmetazole Sodium: White solid. Very soluble in water and in methanol; soluble in acetone; practically insoluble in chloroform.

Cefonicid Sodium: White to off-white solid. Freely soluble in water, in 0.9% sodium chloride solution, and in 5% dextrose solution; soluble in methanol; very slightly soluble in dehydrated alcohol.

Cefoperazone Sodium: White to pale buff crystalline powder. Freely soluble in water; soluble in methanol; slightly soluble in dehydrated alcohol; insoluble in acetone, in ethyl acetate, and in ether.

Ceforanide: White to off-white powder. Very soluble in 1 N sodium hydroxide; practically insoluble in water, in methanol, in chloroform, and in ether.

Cefotaxime Sodium: Off-white to pale yellow crystalline powder. Freely soluble in water; practically insoluble in organic solvents.

Cefoxitin Sodium: White to off-white, granules or powder, having a slight characteristic odor. Is somewhat hygroscopic. Very soluble in water; soluble in methanol; sparingly soluble in dimethylformamide; slightly soluble in acetone; insoluble in ether and in chloroform.

Cefpodoxime Proxetil: White to light brownish-white powder. Odorless or having a faint odor, and has a bitter taste. Freely soluble in dehydrated alcohol; soluble in acetonitrile and in methanol; slightly soluble in ether; very slightly soluble in water.

Ceftazidime: White to cream-colored, crystalline powder. Soluble in alkali and in dimethyl sulfoxide; slightly soluble in dimethylformamide, in methanol, and in water; insoluble in acetone, in alcohol, in chloroform, in dioxane, in ether, in ethyl acetate, and in toluene.

Ceftizoxime Sodium: White to pale yellow crystalline powder. Freely soluble in water.

Ceftriaxone Sodium: White to yellowish-orange crystalline powder. Freely soluble in water; sparingly soluble in methanol; very slightly soluble in alcohol.

Cefuroxime Axetil: White to almost white powder. The amorphous form is freely soluble in acetone; soluble in chloroform, in ethyl acetate, and in methanol; slightly soluble in dehydrated alcohol; insoluble in ether and in water. The crystalline form is freely soluble in acetone; sparingly soluble in chloroform, in ethyl acetate, and in methanol; slightly soluble in dehydrated alcohol; insoluble in ether and in water.

Cefuroxime Sodium: White or faintly yellow powder. Freely soluble in water; soluble in methanol; very slightly soluble in alcohol, in ether, in ethyl acetate, and in chloroform.

Celecoxib: White or almost white, crystalline or amorphous powder. Soluble to freely soluble in ethanol; soluble in methylene chloride; practically insoluble in water.

Cellaburate: Fine white or almost white powder or granules. Available in a range of viscosities, acetyl and butyl contents. Slightly hygroscopic; soluble in acetone, in methylene chloride, in pyridine, and in dimethyl sulfoxide; practically insoluble in water and in alcohol. *NF category:* Coating agent; polymer membrane.

Cellacefate: Free-flowing, white powder. May have a slight odor of acetic acid. Soluble in acetone and in dioxane; insoluble in water and in alcohol. *NF category:* Coating agent.

Cellulose Acetate: Fine, white powder or free-flowing pellets. Available in a range of viscosities and acetyl contents. High viscosity, which reflects high molecular weight, decreases solubility slightly. High acetyl content cellulose acetates generally have more limited solubility in commonly used organic solvents than low acetyl content cellulose acetates, but are more soluble in methylene chloride. All acetyl content cellulose acetates are soluble in dioxane and in dimethylformamide; insoluble in alcohol and in water. *NF category:* Coating agent; polymer membrane.

Microcrystalline Cellulose: Fine, white or almost white powder. It consists of free-flowing, nonfibrous particles. Practically insoluble in sodium hydroxide solution (1 in 20); insoluble in water, in dilute acids, and in most organic solvents. *NF category:* Tablet binder; tablet disintegrant; tablet and/or capsule diluent.

Silicified Microcrystalline Cellulose: White or almost white, very fine to moderately fine powder. It is a free-flowing material that may be compacted into self-binding tablets that disintegrate rapidly in water. Slightly soluble in sodium hydroxide solution (1 in 20); practically insoluble in water, in acetone, in ethanol, in toluene, and in diluted acid. *NF category:* Tablet binder; tablet disintegrant; tablet and/or capsule diluent.

Microcrystalline Cellulose and Carboxymethylcellulose Sodium: Tasteless, odorless, white to off-white, coarse to fine powder. Swells in water, producing, when dispersed, a white, opaque dispersion or gel. Insoluble in organic solvents and in dilute acids. *NF category:* Suspending and/or viscosity-increasing agent.

Oxidized Cellulose: In the form of gauze or lint. Is slightly off-white in color, is acidic to the taste, and has a slight, charred odor. Soluble in dilute alkalies; insoluble in water and in acids.

Oxidized Regenerated Cellulose: A knit fabric, usually in the form of sterile strips. Slightly off-white, having a slight odor. Soluble in dilute alkalies; insoluble in water and in dilute acids.

Powdered Cellulose: White or almost white powder. Exhibits degrees of fineness ranging from a free-flowing dense powder to a coarse, fluffy, nonflowing material. Slightly soluble in sodium hydroxide solution (1 in 20); insoluble in water, in dilute acids, and in nearly all organic

solvents. *NF category:* Filtering aid; sorbent; tablet and/or capsule diluent.

Cellulose Sodium Phosphate: Free-flowing cream-colored, odorless, tasteless powder. Insoluble in water, in dilute acids, and in most organic solvents.

Cephalexin: White to off-white, crystalline powder. Slightly soluble in water; practically insoluble in alcohol, in chloroform, and in ether.

Cephalexin Hydrochloride: White to off-white, crystalline powder. Soluble to the extent of 10 mg per mL in water, in acetone, in acetonitrile, in alcohol, in dimethylformamide, and in methanol; practically insoluble in chloroform, in ether, in ethyl acetate, and in isopropyl alcohol.

Cephalothin Sodium: White to off-white, practically odorless, crystalline powder. Freely soluble in water, in saline TS, and in dextrose solutions; insoluble in most organic solvents.

Cephapirin Benzathine: White, crystalline powder. Soluble in 0.1 N hydrochloric acid; practically insoluble in water, in ether, and in toluene; insoluble in alcohol.

Cephapirin Sodium: White to off-white, crystalline powder, odorless or having a slight odor. Very soluble in water; insoluble in most organic solvents.

Cephadrine: White to off-white, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in chloroform; practically insoluble in ether.

Cetirizine Hydrochloride: White to almost white powder. Freely soluble in water; practically insoluble in acetone and in methylene chloride.

Cetostearyl Alcohol: Unctuous, white flakes or granules, having a faint, characteristic odor, and a bland, mild taste. Soluble in alcohol and in ether; insoluble in water. *NF category:* Stiffening agent.

Cetrimonium Bromide: A white to creamy white, voluminous, free-flowing powder, with a characteristic faint odor and bitter, soapy taste. Freely soluble in water and in alcohol; practically insoluble in ether. *NF category:* Antimicrobial preservative.

Cetyl Alcohol: Unctuous, white flakes, granules, cubes, or castings. Has a faint characteristic odor and a bland, mild taste. Usually melts in the range between 45° and 50°. Soluble in alcohol and in ether, the solubility increasing with an increase in temperature; insoluble in water. *NF category:* Stiffening agent.

Cetyl Esters Wax: White to off-white, somewhat translucent flakes, having a crystalline structure and a pearly luster when caked. Has a faint odor and a bland, mild taste, free from rancidity, and has a specific gravity of about 0.83 at 50°. Soluble in boiling alcohol, in ether, in chloroform, and in fixed and volatile oils; slightly soluble in cold solvent hexane; practically insoluble in cold alcohol; insoluble in water. *NF category:* Stiffening agent.

Cetyl Palmitate: White crystals or flakes. Freely soluble in alcohol and in ether; practically insoluble in water. *NF category:* Stiffening agent.

Cetylpyridinium Chloride: White powder, having a slight, characteristic odor. Very soluble in water, in alcohol, and in chloroform; slightly soluble in benzene and in ether. *NF category:* Antimicrobial preservative; wetting and/or solubilizing agent.

Cetylpyridinium Chloride Topical Solution: Clear liquid. Is colorless unless a color has been added; has an aromatic odor and a bitter taste.

Activated Charcoal: Fine, black, odorless, tasteless powder, free from gritty matter. *NF category:* Sorbent.

Chitosan: White or almost white powder or granules. Soluble in aqueous solutions of glycolic acid, of formic acid, of acetic acid, of hydrochloric acid, and of lactic acid; practically insoluble in organic solvents and in water. *NF category:* Coating agent; film-forming agent; suspending and/or viscosity-increasing agent; vehicle (solid carrier).

Chloral Hydrate: Colorless, transparent, or white crystals having an aromatic, penetrating, and slightly acrid odor, and a slightly bitter, caustic taste. Melts at about 55°, and slowly volatilizes when exposed to air. Very soluble in water and in olive oil; freely soluble in alcohol, in chloroform, and in ether.

Chlorambucil: Off-white, slightly granular powder. Freely soluble in acetone; soluble in dilute alkali; very slightly soluble in water.

Chloramphenicol: Fine, white to grayish-white or yellowish-white, needle-like crystals or elongated plates. Its solutions are practically neutral to litmus. Is reasonably stable in neutral or moderately acid solutions. Its alcohol solution is dextrorotatory and its ethyl acetate solution is levorotatory. Freely soluble in alcohol, in propylene glycol, in acetone, and in ethyl acetate; slightly soluble in water.

Chloramphenicol Palmitate: Fine, white, unctuous, crystalline powder, having a faint odor and a bland, mild taste. Freely soluble in acetone and in chloroform; soluble in ether; sparingly soluble in alcohol; very slightly soluble in solvent hexane; insoluble in water.

Chloramphenicol Sodium Succinate: Light yellow powder. Freely soluble in water and in alcohol.

Chlordiazepoxide: Yellow, practically odorless, crystalline powder. Is sensitive to sunlight. Melts at about 240°. Sparingly soluble in chloroform and in alcohol; insoluble in water.

Chlordiazepoxide Hydrochloride: White or practically white, odorless, crystalline powder. Is affected by sunlight. Soluble in water; sparingly soluble in alcohol; insoluble in solvent hexane.

Chlorhexidine Acetate: A white or almost white, microcrystalline powder. Soluble in alcohol; sparingly soluble in water; slightly soluble in glycerol and in propylene glycol.

Chlorhexidine Gluconate Solution: Almost colorless or pale yellow, clear liquid. Miscible with glacial acetic acid and with water; miscible with three times its volume of acetone and with five times its volume of dehydrated alcohol; further addition of acetone or dehydrated alcohol yields a white turbidity.

Chlorhexidine Hydrochloride: White or almost white, crystalline powder. Sparingly soluble in propylene glycol and in water; very slightly soluble in alcohol.

Chlorobutanol: Colorless to white crystals, having a characteristic, somewhat camphoraceous, odor and taste. Anhydrous form melts at about 95°, and hydrous form melts at about 76°. Freely soluble in alcohol, in ether, in chloroform, and in volatile oils; soluble in glycerin; slightly soluble in water. *NF category:* Antimicrobial preservative.

Chlorocresol: Colorless or practically colorless crystals or crystalline powder, having a characteristic, nontarry odor. Is volatile in steam. Very soluble in alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides; slightly soluble in water and more soluble in hot water. *NF category:* Antimicrobial preservative.

Chloroprocaine Hydrochloride: White, crystalline powder. Is odorless, and is stable in air. Its solutions are acid to litmus. Exhibits local anesthetic properties when placed upon the tongue. Soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in ether.

Chloroquine: White or slightly yellow, crystalline powder. Is odorless, and has a bitter taste. Soluble in dilute acids, in chloroform, and in ether; very slightly soluble in water.

Chloroquine Hydrochloride Injection: Colorless liquid.

Chloroquine Phosphate: White, crystalline powder. Is odorless, has a bitter taste, and is discolored slowly on exposure to light. Its solutions have a pH of about 4.5. Exists in two polymorphic forms, one melting between 193° and 195° and the other between 210° and 215° (see *Melting*

Range or Temperature <741>); mixture of the forms melts between 193° and 215°. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether.

Chlorothiazide: White or practically white, crystalline, odorless powder. Melts at about 340°, with decomposition. Freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly soluble in methanol and in pyridine; practically insoluble in ether, in benzene, and in chloroform; very slightly soluble in water.

Chloroxylonol: White crystals or crystalline powder, having a characteristic odor. Is volatile in steam. Freely soluble in alcohol, in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides; very slightly soluble in water.

Chlorpheniramine Maleate: White, odorless, crystalline powder. Its solutions have a pH between 4 and 5. Freely soluble in water; soluble in alcohol and in chloroform; slightly soluble in ether and in benzene.

Chlorpromazine: White, crystalline solid, having an amine-like odor. Darkens on prolonged exposure to light. Melts at about 60°. Freely soluble in alcohol, in benzene, in chloroform, in ether, and in dilute mineral acids; practically insoluble in water and in dilute alkali hydroxides.

Chlorpromazine Hydrochloride: White or slightly creamy white, odorless, crystalline powder. Darkens on prolonged exposure to light. Very soluble in water; freely soluble in alcohol and in chloroform; insoluble in ether and in benzene.

Chlorpropamide: White, crystalline powder, having a slight odor. Soluble in alcohol; sparingly soluble in chloroform; practically insoluble in water.

Chlortetracycline Hydrochloride: Yellow, crystalline powder. Is odorless, and has a bitter taste. Is stable in air, but is slowly affected by light. Soluble in solutions of alkali hydroxides and carbonates; sparingly soluble in water; slightly soluble in alcohol; practically insoluble in acetone, in chloroform, in dioxane, and in ether.

Chlorthalidone: White to yellowish-white, crystalline powder. Melts at a temperature above 215°, with decomposition. Soluble in methanol; slightly soluble in alcohol; practically insoluble in water, in ether, and in chloroform.

Chlorzoxazone: White or practically white, practically odorless, crystalline powder. Soluble in solutions of alkali hydroxides and ammonia; sparingly soluble in alcohol, in isopropyl alcohol, and in methanol; slightly soluble in water.

Cholecalciferol: White, odorless crystals. Is affected by air and by light. Melts at about 85°. Soluble in alcohol, in chloroform, and in fatty oils; insoluble in water.

Cholesterol: White or faintly yellow, practically odorless, pearly leaflets, needles, powder, or granules. Acquires a yellow to pale tan color on prolonged exposure to light. Soluble in acetone, in chloroform, in dioxane, in ether, in ethyl acetate, in solvent hexane, and in vegetable oils; sparingly soluble in dehydrated alcohol; slightly (and slowly) soluble in alcohol; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Cholestyramine Resin: White to buff-colored, hygroscopic, fine powder. Is odorless or has not more than a slight amine-like odor. Insoluble in water, in alcohol, in chloroform, and in ether.

Choline Bitartrate: White, hygroscopic, crystalline powder. Clear, colorless liquid in solution. Melts between 148° and 153°. Is odorless, or may have a faint trimethylamine odor. Freely soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform.

Choline Chloride: Colorless or white crystals or crystalline powder, usually having a slight odor of trimethylamine. Clear and colorless in solution. Hygroscopic. Soluble in alcohol and in water.

Sodium Chromate Cr 51 Injection: Clear, slightly yellow solution.

Chromic Chloride: Dark green, odorless, slightly deliquescent crystals. Soluble in water and in alcohol; slightly soluble in acetone; practically insoluble in ether.

Chymotrypsin: White to yellowish-white, crystalline or amorphous, odorless, powder. An amount equivalent to 100,000 USP Units is soluble in 10 mL of water and in 10 mL of saline TS.

Ciclopirox: White to slightly yellowish-white, crystalline powder. Freely soluble in ethanol and in methylene chloride; soluble in ether; slightly soluble in water.

Ciclopirox Olamine: White to slightly yellowish-white, crystalline powder. Very soluble in alcohol and in methylene chloride; slightly soluble in water; practically insoluble in cyclohexane.

Cilastatin Sodium: White to tan-colored powder. Soluble in water and in methanol.

Cilostazol: White to off-white crystals. Freely soluble in chloroform; slightly soluble in methanol and in alcohol; practically insoluble in water.

Cimetidine: White to off-white, crystalline powder; odorless, or having a slight mercaptan odor. Freely soluble in methanol; soluble in alcohol and in polyethylene glycol 400; sparingly soluble in isopropyl alcohol; slightly soluble in water and in chloroform; practically insoluble in ether.

Cinoxacin: White to yellowish-white, crystalline solid. Is odorless, and has a bitter taste and a lingering aftertaste. Soluble in alkaline solution; insoluble in water and in most common organic solvents.

Ciprofloxacin Hydrochloride: Faintly yellowish to light yellow crystals. Sparingly soluble in water; slightly soluble in acetic acid and in methanol; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane, and in methylene chloride.

Cisapride: White or almost white powder. Freely soluble in dimethylformamide; soluble in methylene chloride; sparingly soluble in methanol; practically insoluble in water.

Change to read:

Citalopram Hydrobromide: White to almost white, crystalline powder. Soluble in alcohol; sparingly soluble in water and in dehydrated alcohol. ▲USP36

Anhydrous Citric Acid: Colorless, translucent crystals, or white, granular to fine, crystalline powder. Melts at about 153°, with decomposition. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether. *NF category:* Acidifying agent; buffering agent.

Citric Acid Monohydrate: Colorless, translucent crystals, or white, granular to fine, crystalline powder. Efflorescent in dry air. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether. *NF category:* Acidifying agent; buffering agent.

Clarithromycin: White to off-white, crystalline powder. Soluble in acetone; slightly soluble in dehydrated alcohol, in methanol, and in acetonitrile, and in phosphate buffer at pH values of 2 to 5; practically insoluble in water.

Clavulanate Potassium: White to off-white powder. Is moisture-sensitive. Freely soluble in water, but stability in aqueous solution is not good, optimum stability at a pH of 6.0 to 6.3; soluble in methanol, with decomposition.

Clemastine Fumarate: White to off-white, odorless powder. Its solutions are acid to litmus. Slightly soluble in methanol; very slightly soluble in water, and in chloroform.

Clenbuterol Hydrochloride: White or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in acetone. It melts with decomposition at 173°.

Clidinium Bromide: White to nearly white, practically odorless, crystalline powder. Is optically inactive. Melts at about 242°. Soluble in water and in alcohol; slightly soluble in benzene and in ether.

Clindamycin Hydrochloride: White or practically white, crystalline powder. Is odorless or has a faint mercaptan-like odor. Is stable in the presence of air and light. Its solutions are acidic and are dextrorotatory. Freely soluble in water, in dimethylformamide, and in methanol; soluble in alcohol; practically insoluble in acetone.

Clindamycin Palmitate Hydrochloride: White to off-white amorphous powder, having a characteristic odor. Very soluble in ethyl acetate and in dimethylformamide; freely soluble in water, in benzene, in ether, in chloroform, and in alcohol.

Clindamycin Phosphate: White to off-white, hygroscopic, crystalline powder. Is odorless or practically odorless, and has a bitter taste. Freely soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in acetone; practically insoluble in chloroform, in benzene, and in ether.

Clioquinol: Voluminous, spongy, yellowish-white to brownish-yellow powder, having a slight, characteristic odor. Darkens on exposure to light. Melts at about 180°, with decomposition. Soluble in hot ethyl acetate and in hot glacial acetic acid; practically insoluble in water and in alcohol.

Clobetasol Propionate: White to cream, crystalline powder. Soluble in acetone, in dimethyl sulfoxide, in chloroform, in methanol, and in dioxane; sparingly soluble in ethanol; slightly soluble in benzene and in diethyl ether; practically insoluble in water.

Clocortolone Pivalate: White to yellowish-white, odorless powder. Melts at about 230°, with decomposition. Freely soluble in chloroform and in dioxane; soluble in acetone; sparingly soluble in alcohol; slightly soluble in benzene and in ether.

Clofazimine: Dark red crystals. Melts at about 217°, with decomposition. Soluble in chloroform and in benzene; sparingly soluble in alcohol, in acetone, and in ethyl acetate; practically insoluble in water.

Clofibrate: Colorless to pale yellow liquid having a characteristic odor. Soluble in acetone, in alcohol, in benzene, and in chloroform; insoluble in water.

Clomiphene Citrate: White to pale yellow, essentially odorless powder. Freely soluble in methanol; sparingly soluble in alcohol; slightly soluble in water and in chloroform; insoluble in ether.

Clomipramine Hydrochloride: White to faintly yellow, crystalline powder. Very soluble in water.

Clonazepam: Light yellow powder, having a faint odor. Sparingly soluble in acetone and in chloroform; slightly soluble in alcohol and in ether; insoluble in water.

Clonidine: White to almost white, crystalline powder. Melting point is about 130°. Freely soluble in methanol and in alcohol.

Change to read:

Clodigrel Bisulfate: White to off-white powder. ▲Freely soluble at pH 1; practically insoluble at neutral pH.▲*USP36*

Cloprostenol Sodium: White or almost white, amorphous powder. Is hygroscopic. Freely soluble in water, in alcohol, and in methanol; practically insoluble in acetone.

Clorazepate Dipotassium: Light yellow, crystalline powder. Darkens on exposure to light. Soluble in water but, upon standing, may precipitate from the solution; slightly soluble in alcohol and in isopropyl alcohol; practically insoluble in acetone, in benzene, in chloroform, in ether, and in methylene chloride.

Clorsulon: White to off-white powder. Freely soluble in acetonitrile and in methanol; slightly soluble in water; very slightly soluble in methylene chloride.

Clotrimazole: White to pale yellow, crystalline powder. Melts at about 142°, with decomposition. Freely soluble in methanol, in acetone, in chloroform, and in alcohol; practically insoluble in water.

Cloxacillin Benzathine: White or almost white, almost odorless, crystals or crystalline powder. Soluble in chloroform and in methanol; sparingly soluble in acetone; slightly soluble in water, in alcohol, and in isopropyl alcohol.

Cloxacillin Sodium: White, odorless, crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform.

Clozapine: Yellow, crystalline powder. Soluble in chloroform, in acetone, and in alcohol; sparingly soluble in acetonitrile; insoluble in water.

Coal Tar: Nearly black, viscous liquid, heavier than water, having a characteristic, naphthalene-like odor, and producing a sharp, burning sensation on the tongue. Slightly soluble in water, to which it imparts its characteristic odor and taste and a faintly alkaline reaction; partially soluble in acetone, in alcohol, in carbon disulfide, in chloroform, in ether, in methanol, and in solvent hexane; soluble in benzene and nitrobenzene.

Cyanocobalamin Co 57 Capsules: May contain a small amount of solid or solids, or may appear empty.

Cyanocobalamin Co 57 Oral Solution: Clear, colorless to pink solution.

Cocaine: Colorless to white crystals or white, crystalline powder. Is levorotatory in 3 N hydrochloric acid solution. Its saturated solution is alkaline to litmus. Very soluble in warm alcohol; freely soluble in alcohol, in chloroform, and in ether; soluble in olive oil; sparingly soluble in mineral oil; slightly soluble in water.

Cocaine Hydrochloride: Colorless crystals or white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in chloroform and in glycerin; insoluble in ether.

Coccidioidin: Clear, practically colorless or amber-colored liquid.

Cocoa Butter: Yellowish-white solid, having a faint, agreeable odor, and a bland, chocolate-like taste if the cocoa butter is obtained by pressing. If obtained by extraction, the taste is bland. Is usually brittle at temperatures below 25°. Freely soluble in ether and in chloroform; soluble in boiling dehydrated alcohol; slightly soluble in alcohol. *NF category:* Suppository base.

Coconut Oil: Clear, white to light yellow-tan, viscous liquid. Freely soluble in methylene chloride and in light petroleum (bp: 65° to 70°); very slightly soluble in alcohol; practically insoluble in water. *NF category:* Coating agent; emulsifying and/or solubilizing agent.

Hydrogenated Coconut Oil: White to yellowish, fatty solid to semi-solid. Freely soluble in ether; very slightly soluble in alcohol; practically insoluble in water. *NF category:* Coating agent; tablet binder; tablet and/or capsule lubricant.

Cod Liver Oil: Thin, oily liquid, having a characteristic, slightly fishy but not rancid odor, and a fishy taste. Freely soluble in ether, in chloroform, in carbon disulfide, and in ethyl acetate; slightly soluble in alcohol.

Codeine: Colorless or white crystals or white, crystalline powder. It effloresces slowly in dry air, and is affected by light. In acid or alcohol solutions it is levorotatory. Its saturated solution is alkaline to litmus. Very soluble in chloroform; freely soluble in alcohol; sparingly soluble in ether; slightly soluble in water. When heated in an amount of water insufficient for complete solution, it melts to oily drops that crystallize on cooling.

Codeine Phosphate: Fine, white, needle-shaped crystals, or white, crystalline powder. Is odorless. Is affected by light. Its solutions are acid to litmus. Very soluble in hot

water; freely soluble in water; slightly soluble in alcohol but more so in boiling alcohol.

Codeine Sulfate: White crystals, usually needle-like, or white, crystalline powder. Is affected by light. Freely soluble in water at 80°; soluble in water; very slightly soluble in alcohol; insoluble in chloroform and in ether.

Colchicine: Pale yellow to pale greenish-yellow, amorphous scales, or powder or crystalline powder. Is odorless or nearly so, and darkens on exposure to light. Freely soluble in alcohol and in chloroform; soluble in water; slightly soluble in ether.

Colestipol Hydrochloride: Yellow to orange beads. Swells but does not dissolve in water or dilute aqueous solutions of acid or alkali. Insoluble in the common organic solvents.

Colistimethate Sodium: White to slightly yellow, odorless, fine powder. Freely soluble in water; soluble in methanol; insoluble in acetone and in ether.

Colistin Sulfate: White to slightly yellow, odorless, fine powder. Freely soluble in water; slightly soluble in methanol; insoluble in acetone and in ether.

Collodion: Clear, or slightly opalescent, viscous liquid. Is colorless, or slightly yellowish, and has the odor of ether.

Flexible Collodion: Clear, or slightly opalescent, viscous liquid. Is colorless or slightly yellow, and has the odor of ether. The strong odor of camphor becomes noticeable as the ether evaporates.

Copovidone: White to yellowish-white powder or flakes. Is hygroscopic. Freely soluble in water, in alcohol, and in methylene chloride; practically insoluble in ether. *NF category:* Tablet binder; coating agent.

Corn Oil: Clear, light yellow, oily liquid, having a faint, characteristic odor and taste. Slightly soluble in alcohol. Miscible with ether, with chloroform, with benzene, and with solvent hexane. *Specific gravity* (841): Between 0.914 and 0.921. *NF category:* Solvent; vehicle (oleaginous).

Corn Syrup: Clear, white to light yellow, viscous liquid. Is miscible in all proportions with water. *NF category:* Suspending and/or viscosity-increasing agent; sweetening agent; tablet and/or capsule diluent; tablet binder; tonicity agent.

Corn Syrup Solids: Sweet, white to light yellow powder or granules. Soluble in water. *NF category:* Coating agent; flavored and/or sweetened vehicle; humectant; solid carrier; suspending and/or viscosity-increasing agent; sweetening agent; tablet and/or capsule diluent; tablet binder; tonicity agent.

Corticotropin Injection: Colorless or light straw-colored liquid.

Corticotropin for Injection: White or practically white, soluble, amorphous solid having the characteristic appearance of substances prepared by freeze-drying.

Repository Corticotropin Injection: Colorless or light straw-colored liquid, which may be quite viscous at room temperature. Is odorless or has an odor of an antimicrobial agent.

Corticotropin Zinc Hydroxide Injectable Suspension: Flocculent, white, aqueous suspension, free from large particles following moderate shaking.

Cortisone Acetate: White or practically white, odorless, crystalline powder. Is stable in air. Melts at about 240°, with some decomposition (see *Melting Range or Temperature* (741)). Freely soluble in chloroform; soluble in dioxane; sparingly soluble in acetone; slightly soluble in alcohol; insoluble in water.

Purified Cotton: White, soft, fine filament-like hairs appearing under the microscope as hollow, flattened, and twisted bands, striate and slightly thickened at the edges. Is practically odorless and practically tasteless. Soluble in ammoniated cupric oxide TS; insoluble in ordinary solvents.

Cottonseed Oil: Pale yellow, oily liquid. Is odorless or nearly so, and has a bland taste. At temperatures below 10° particles of solid fat may separate from the Oil, and at about 0° to –5° the Oil becomes a solid or nearly so. *Specific gravity* (841): Between 0.915 and 0.921. Slightly soluble in alcohol. Miscible with ether, with chloroform, with solvent hexane, and with carbon disulfide. *NF category:* Solvent; vehicle (oleaginous).

Hydrogenated Cottonseed Oil: A white mass or powder that melts to a clear, pale yellow liquid when heated. Freely soluble in methylene chloride and in toluene; very slightly soluble in alcohol; practically insoluble in water.

Creatinine: White crystals or crystalline powder; odorless. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone, in ether, and in chloroform. *NF category:* Bulking agent for freeze-drying.

Cresol: Colorless, or yellowish to brownish-yellow, or pinkish, highly refractive liquid, becoming darker with age and on exposure to light. Has a phenol-like, sometimes empyreumatic odor. A saturated solution of it is neutral or only slightly acid to litmus. Sparingly soluble in water, usually forming a cloudy solution; dissolves in solutions of fixed alkali hydroxides. Miscible with alcohol, with ether, and with glycerin. *NF category:* Antimicrobial preservative.

Cromolyn Sodium: White, odorless, crystalline powder. Is tasteless at first, with a slightly bitter aftertaste. Is hygroscopic. Soluble in water; insoluble in alcohol and in chloroform.

Cromolyn Sodium for Inhalation: White to creamy white, odorless, hygroscopic, and very finely divided powder.

Croscarmellose Sodium: White, free-flowing powder. Partially soluble in water; insoluble in alcohol, in ether, and in other organic solvents. *NF category:* Tablet disintegrant.

Crospovidone: White to creamy-white, hygroscopic powder, having a faint odor. Insoluble in water and in ordinary organic solvents. *NF category:* Tablet disintegrant.

Crotamiton: Colorless to slightly yellowish oil, having a faint amine-like odor. Soluble in alcohol and in methanol.

Cupric Chloride: Bluish green, deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether.

Cupric Sulfate: Deep blue, triclinic crystals or blue, crystalline granules or powder. It effloresces slowly in dry air. Its solutions are acid to litmus. Very soluble in boiling water; freely soluble in water and in glycerin; slightly soluble in alcohol.

Cyanocobalamin: Dark red crystals or amorphous or crystalline red powder. In the anhydrous form, it is very hygroscopic and when exposed to air it may absorb about 12% of water. Soluble in alcohol; sparingly soluble in water; insoluble in acetone, in chloroform, and in ether.

Cyclandelate: White, crystalline powder. Very soluble in acetonitrile, in alcohol, and in ether; practically insoluble in water. Melts at about 58°.

Cyclizine Hydrochloride: White, crystalline powder or small, colorless crystals. Is odorless or nearly so, and has a bitter taste. Melts indistinctly at about 285°, with decomposition. Sparingly soluble in chloroform; slightly soluble in water and in alcohol; insoluble in ether.

Cyclobenzaprine Hydrochloride: White to off-white, odorless, crystalline powder. Freely soluble in water, in alcohol, and in methanol; sparingly soluble in isopropanol; slightly soluble in chloroform and in methylene chloride; insoluble in hydrocarbons.

Cyclopentolate Hydrochloride: White, crystalline powder, which upon standing develops a characteristic odor. Its solutions are acid to litmus. Melts at about 138°, the melt appearing opaque. Very soluble in water; freely soluble in alcohol; insoluble in ether.

Cyclophosphamide: White, crystalline powder. Liquefies upon loss of its water of crystallization. Soluble in water and in alcohol.

Cyclopropane: Colorless gas having a characteristic odor. Has a pungent taste. One L at a pressure of 760 mm and a temperature of 0° weighs about 1.88 g. One volume dissolves in about 2.7 volumes of water at 15°. Freely soluble in alcohol; soluble in fixed oils.

Cycloserine: White to pale yellow, crystalline powder. Is odorless or has a faint odor. Is hygroscopic and deteriorates upon absorbing water. Its solutions are dextrorotatory. Freely soluble in water.

Cyclosporine: White to almost white powder. Soluble in acetone, in alcohol, in methanol, in ether, in chloroform, and in methylene chloride; slightly soluble in saturated hydrocarbons; practically insoluble in water.

Cyproheptadine Hydrochloride: White to slightly yellow, odorless or practically odorless, crystalline powder. Freely soluble in methanol; soluble in chloroform; sparingly soluble in alcohol; slightly soluble in water; practically insoluble in ether.

Cyromazine: White or off-white, odorless, crystalline powder. Slightly soluble in methanol and in water.

Cysteine Hydrochloride: White crystals or crystalline powder. Soluble in water, in alcohol, and in acetone.

Cytarabine: Odorless, white to off-white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in chloroform.

Dactinomycin: Bright red, crystalline powder. Is somewhat hygroscopic and is affected by light and by heat. Freely soluble in alcohol; soluble in water at 10° and slightly soluble in water at 37°; very slightly soluble in ether.

Danazol: White to pale yellow, crystalline powder. Melts at about 225°, with some decomposition. Freely soluble in chloroform; soluble in acetone; sparingly soluble in alcohol and in benzene; slightly soluble in ether; practically insoluble or insoluble in water and in hexane.

Change to read:

Dantrolene Sodium: Fine orange to orange-brown powder. Sparingly soluble in ▲dimethylformamide and in glycerine; sparingly soluble to practically insoluble in acetone.▲^{USP36}

Dapsone: White or creamy white, crystalline powder. Is odorless and has a slightly bitter taste. Freely soluble in alcohol; soluble in acetone and in dilute mineral acids; very slightly soluble in water.

Daunorubicin Hydrochloride: Orange-red, crystalline, hygroscopic powder. Freely soluble in water and in methanol; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in acetone.

Deferoxamine Mesylate: White to off-white powder. Freely soluble in water; slightly soluble in methanol.

Dehydrocholic Acid: White, fluffy, odorless powder, having a bitter taste. Soluble in glacial acetic acid and in solutions of alkali hydroxides and carbonates; sparingly soluble in chloroform (the solutions in alcohol and in chloroform usually are slightly turbid); slightly soluble in alcohol and in ether; practically insoluble in water.

Dehydroacetic Acid: White or nearly white, crystalline powder. Soluble in aqueous solutions of alkalies; very slightly soluble in water. One g of sample dissolves in about 35 mL of alcohol and in 5 mL of acetone. *NF category:* Antimicrobial preservative.

Demecarium Bromide: White or slightly yellow, slightly hygroscopic, crystalline powder. Freely soluble in water and in alcohol; soluble in ether; sparingly soluble in acetone.

Demeclocycline: Yellow, crystalline, odorless powder, having a bitter taste. Soluble in alcohol; sparingly soluble in

water. Dissolves readily in 3 N hydrochloric acid and in alkaline solutions.

Demeclocycline Hydrochloride: Yellow, crystalline, odorless powder, having a bitter taste. Sparingly soluble in water and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in acetone and in chloroform.

Denatonium Benzoate: Very soluble in chloroform and in methanol; freely soluble in water and in alcohol; very slightly soluble in ether. *NF category:* Alcohol denaturant.

Desipramine Hydrochloride: White to off-white, crystalline powder. Melts at about 213°. Freely soluble in methanol and in chloroform; soluble in water and in alcohol; insoluble in ether.

Desmopressin Acetate: White, fluffy powder. Soluble in water, in alcohol, and in acetic acid.

Desoximetasone: White to practically white, odorless, crystalline powder. Freely soluble in alcohol, in acetone, and in chloroform; insoluble in water.

Desoxycholic Acid: Occurs as a white, crystalline powder. Freely soluble in alcohol; soluble in acetone and in solutions of alkali hydroxides and carbonates; slightly soluble in chloroform and in ether; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Desoxycorticosterone Acetate: White or creamy white, crystalline powder. Is odorless, and is stable in air. Sparingly soluble in alcohol, in acetone, and in dioxane; slightly soluble in vegetable oils; practically insoluble in water.

Dexamethasone: White to practically white, odorless, crystalline powder. Is stable in air. Melts at about 250°, with some decomposition. Sparingly soluble in acetone, in alcohol, in dioxane, and in methanol; slightly soluble in chloroform; very slightly soluble in ether; practically insoluble in water.

Dexamethasone Acetate: Clear, white to off-white, odorless powder. Freely soluble in methanol, in acetone, and in dioxane; practically insoluble in water.

Dexamethasone Sodium Phosphate: White or slightly yellow, crystalline powder. Is odorless or has a slight odor of alcohol, and is exceedingly hygroscopic. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dioxane; insoluble in chloroform and in ether.

Dexbrompheniramine Maleate: White, odorless, crystalline powder. Exists in two polymorphic forms, one melting between 106° and 107° and the other between 112° and 113°. Mixtures of the forms may melt between 105° and 113°. The pH of a solution (1 in 100) is about 5. Freely soluble in water; soluble in alcohol and in chloroform.

Dexchlorpheniramine Maleate: White, odorless, crystalline powder. Freely soluble in water; soluble in alcohol and in chloroform; slightly soluble in benzene and in ether.

Dexpantenol: Clear, viscous, somewhat hygroscopic liquid, having a slight, characteristic odor. Some crystallization may occur on standing. Freely soluble in water, in alcohol, in methanol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerin.

Dextran 1: A white to off-white powder. Is hygroscopic. Very soluble in water; sparingly soluble in alcohol.

Dextrates: Free-flowing, porous, white, odorless, spherical granules consisting of aggregates of microcrystals, having a sweet taste and producing a cooling sensation in the mouth. May be compressed directly into self-binding tablets. Freely soluble in water (heating increases its solubility in water); soluble in dilute acids and alkalies and in basic organic solvents such as pyridine; insoluble in the common organic solvents. *NF category:* Sweetening agent; tablet and/or capsule diluent.

Dextrin: Free-flowing, white, yellow, or brown powder. Its solubility in water varies; it is usually very soluble, but often contains an insoluble portion. *NF category:* Tablet binder; tablet and/or capsule diluent.

Dextroamphetamine Sulfate: White, odorless, crystalline powder. Soluble in water; slightly soluble in alcohol; insoluble in ether.

Dextromethorphan: Practically white to slightly yellow, odorless, crystalline powder. Eleven mg of Dextromethorphan is equivalent to 15 mg of dextromethorphan hydrobromide monohydrate. Freely soluble in chloroform; practically insoluble in water.

Dextromethorphan Hydrobromide: Practically white crystals or crystalline powder, having a faint odor. Melts at about 126°, with decomposition. Freely soluble in alcohol and in chloroform; sparingly soluble in water; insoluble in ether.

Dextrose: Colorless crystals or white, crystalline or granular powder. Is odorless, and has a sweet taste. Very soluble in boiling water; freely soluble in water; soluble in boiling alcohol; slightly soluble in alcohol. *NF category:* Sweetening agent; tonicity agent; vehicle (flavored and/or sweetened).

Dextrose Excipient: Colorless crystals or white, crystalline or granular powder. Is odorless and sweet-tasting. Very soluble in boiling water; freely soluble in water; sparingly soluble in boiling alcohol; slightly soluble in alcohol. *NF category:* Sweetening agent; tablet and/or capsule diluent.

Diacetylated Monoglycerides: Clear liquid. Very soluble in 80% (w/w) aqueous alcohol, in vegetable oils, and in mineral oils; sparingly soluble in 70% alcohol. *NF category:* Plasticizer.

Diatrizoate Meglumine: White, odorless powder. Freely soluble in water.

Diatrizoate Meglumine Injection: Clear, colorless to pale yellow, slightly viscous liquid.

Diatrizoate Meglumine and Diatrizoate Sodium Injection: Clear, colorless to pale yellow, slightly viscous liquid. May crystallize at room temperature or below.

Diatrizoate Sodium: White, odorless powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether.

Diatrizoate Sodium Injection: Clear, colorless to pale yellow, slightly viscous liquid.

Diatrizoate Sodium Solution: Clear, pale yellow to light brown liquid.

Diatrizoic Acid: White, odorless powder. Soluble in dimethylformamide and in alkali hydroxide solutions; very slightly soluble in water and in alcohol.

Diazepam: Off-white to yellow, practically odorless, crystalline powder. Freely soluble in chloroform; soluble in alcohol; practically insoluble in water.

Diazoxide: White or cream-white crystals or crystalline powder. Very soluble in strong alkaline solutions; freely soluble in dimethylformamide; sparingly soluble to practically insoluble in water and in most organic solvents.

Dibucaine: White to off-white powder, having a slight, characteristic odor. Darkens on exposure to light. Soluble in 1 N hydrochloric acid and in ether; slightly soluble in water.

Dibucaine Hydrochloride: Colorless or white to off-white crystals or white to off-white, crystalline powder. Is odorless, is somewhat hygroscopic, and darkens on exposure to light. Its solutions have a pH of about 5.5. Freely soluble in water, in alcohol, in acetone, and in chloroform.

Dibutyl Phthalate: A clear, oily liquid, colorless or very slightly yellow. Practically insoluble in water. Miscible with alcohol and with ether.

Dibutyl Sebacate: Colorless, oily liquid of very mild odor. Soluble in alcohol, in isopropyl alcohol, and in mineral oil; very slightly soluble in propylene glycol; practically insoluble in water and in glycerin. *NF category:* Plasticizer.

Dichloralphenazone: White, microcrystalline powder. Has a slight odor characteristic of chloral hydrate. Decomposed by dilute alkali, liberating chloroform. Freely soluble

in water, in alcohol, and in chloroform; soluble in dilute acids.

Dichlorodifluoromethane: Clear, colorless gas, having a faint, ethereal odor. Its vapor pressure at 25° is about 4880 mm of mercury (80 psig). *NF category:* Aerosol propellant.

Dichlorotetrafluoroethane: Clear, colorless gas, having a faint, ethereal odor. Its vapor pressure at 25° is about 1620 mm of mercury (17 psig). Usually contains between 6% and 10% of its isomer, CCl₂F-CF₃. *NF category:* Aerosol propellant.

Diethylazuril: White to yellow powder. Sparingly soluble in dimethylformamide; practically insoluble in water, in alcohol, and in methylene chloride.

Diclofenac Potassium: White to off-white or slightly yellowish crystalline powder, slightly hygroscopic. Freely soluble in methanol; soluble in alcohol; sparingly soluble in water; slightly soluble in acetone.

Diclofenac Sodium: White to off-white, hygroscopic, crystalline powder. Melts at about 284°. Freely soluble in methanol; soluble in ethanol; sparingly soluble in water; practically insoluble in chloroform and in ether.

Dicloxacillin Sodium: White to off-white, crystalline powder. Freely soluble in water.

Dicyclomine Hydrochloride: Fine, white, crystalline powder. Is practically odorless and has a very bitter taste. Freely soluble in alcohol and in chloroform; soluble in water; very slightly soluble in ether.

Dicyclomine Hydrochloride Injection: Colorless solution, which may have the odor of a preservative.

Didanosine: White to off-white, crystalline powder. Very soluble in dimethyl sulfoxide; practically insoluble or insoluble in acetone and in methanol.

Dienestrol: Colorless, white or practically white, needle-like crystals, or white or practically white, crystalline powder. Is odorless. Soluble in alcohol, in acetone, in ether, in methanol, in propylene glycol, and in solutions of alkali hydroxides; slightly soluble in chloroform and in fatty oils; practically insoluble in water.

Diethanolamine: White or clear, colorless crystals, deliquescent in moist air; or colorless liquid. Miscible with water, with alcohol, with acetone, with chloroform, and with glycerin. Slightly soluble to insoluble in benzene, in ether, and in petroleum ether. *NF category:* Alkalizing agent; emulsifying and/or solubilizing agent.

Diethylcarbamazine Citrate: White, crystalline powder. Melts at about 136°, with decomposition. Is odorless or has a slight odor; is slightly hygroscopic. Very soluble in water; sparingly soluble in alcohol; practically insoluble in acetone, in chloroform, and in ether.

Diethylene Glycol Monoethyl Ether: Clear, colorless liquid. Is hygroscopic. Miscible with water, with acetone, and with alcohol; partially miscible with vegetable oils; immiscible with mineral oils. Specific gravity about 0.991. *NF category:* Ointment base; solvent.

Diethylene Glycol Stearates: White or almost white, waxy solid. Soluble in acetone and in hot alcohol; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Diethyl Phthalate: Colorless, practically odorless, oily liquid. Insoluble in water. Miscible with alcohol, with ether, and with other usual organic solvents. *NF category:* Plasticizer.

Add the following:

▲**Diethyl Sebacate:** A colorless to slightly yellow liquid. Miscible with alcohol, with ether, with other organic solvents, and with most fixed oils; insoluble or practically insoluble in water. *NF category:* Flavors and perfumes. ▲*NF31*

Diethylpropion Hydrochloride: White to off-white, fine crystalline powder. Is odorless, or has a slight characteristic odor. It melts at about 175°, with decomposition. Freely soluble in water, in chloroform, and in alcohol; practically insoluble in ether.

Diethylstilbestrol: White, odorless, crystalline powder. Soluble in alcohol, in chloroform, in ether, in fatty oils, and in dilute alkali hydroxides; practically insoluble in water.

Diethyltoluamide: Colorless liquid, having a faint, pleasant odor. Boils at about 111° under a pressure of 1 mm of mercury. Practically insoluble in water and in glycerin. Miscible with alcohol, with isopropyl alcohol, with ether, with chloroform, and with carbon disulfide.

Diflurasone Diacetate: White to pale yellow, crystalline powder. Soluble in methanol and in acetone; sparingly soluble in ethyl acetate; slightly soluble in toluene; very slightly soluble in ether; insoluble in water.

Diflunisal: White to off-white, practically odorless powder. Freely soluble in alcohol and in methanol; soluble in acetone and in ethyl acetate; slightly soluble in chloroform, in carbon tetrachloride, and in methylene chloride; insoluble in hexane and in water.

Digitoxin: White or pale buff, odorless, microcrystalline powder. Sparingly soluble in chloroform; slightly soluble in alcohol; very slightly soluble in ether; practically insoluble in water.

Digoxin: Clear to white, odorless crystals or white, odorless crystalline powder. Freely soluble in pyridine; slightly soluble in diluted alcohol and in chloroform; practically insoluble in water and in ether.

Dihydroergotamine Mesylate: White to slightly yellowish powder, or off-white to faintly red powder, having a faint odor. Soluble in alcohol; slightly soluble in water and in chloroform.

Dihydrostreptomycin Sulfate: White or almost white, amorphous or crystalline powder. Amorphous form is hygroscopic. Freely soluble in water; practically insoluble in acetone, in chloroform, and in methanol.

Dihydrotachysterol: Colorless or white, odorless crystals, or white, odorless, crystalline powder. Freely soluble in ether and in chloroform; soluble in alcohol; sparingly soluble in vegetable oils; practically insoluble in water.

Dihydroxyacetone: White to off-white crystalline powder. The monomeric form is freely soluble in water, in alcohol, and in ether. The dimeric form is freely soluble in water; soluble in alcohol; and sparingly soluble in ether.

Dihydroxyaluminum Aminoacetate: White, odorless powder having a faintly sweet taste. Soluble in dilute mineral acids and in solutions of fixed alkalies; insoluble in water and in organic solvents.

Dihydroxyaluminum Aminoacetate Magma: White, viscous suspension, from which small amounts of water may separate on standing.

Dihydroxyaluminum Sodium Carbonate: Fine, white, odorless powder. Soluble in dilute mineral acids with the evolution of carbon dioxide; practically insoluble in water and in organic solvents.

Diloxanide Furoate: White or almost white, crystalline powder. Freely soluble in chloroform; slightly soluble in alcohol and in ether; very slightly soluble in water.

Diltiazem Hydrochloride: White, odorless, crystalline powder or small crystals. Freely soluble in chloroform, in formic acid, in methanol, and in water; sparingly soluble in dehydrated alcohol; insoluble in ether. Melts at about 210°, with decomposition.

Dimenhydrinate: White, crystalline, odorless powder. Freely soluble in alcohol and in chloroform; sparingly soluble in ether; slightly soluble in water.

Dimercaprol: Colorless or practically colorless liquid, having a disagreeable, mercaptan-like odor. Soluble in water, in alcohol, in benzyl benzoate, and in methanol.

Dimercaprol Injection: Yellow, viscous solution having a pungent, disagreeable odor. Specific gravity is about 0.978.

Dimethicone: A clear, colorless, and odorless liquid. Soluble in chlorinated hydrocarbons, in benzene, in toluene, in xylene, in *n*-hexane, in petroleum spirits, in ether, and in amyl acetate; very slightly soluble in isopropyl alcohol; insoluble in water, in methanol, in alcohol, and in acetone. *NF* category: Antifoaming agent; water repelling agent.

Dimethyl Sulfoxide: Clear, colorless, odorless, hygroscopic liquid. Melts at about 18.4°. Boils at about 189°. Soluble in water; practically insoluble in acetone, in alcohol, in benzene, in chloroform, and in ether.

Dinoprostone: White to off-white, crystalline powder. Freely soluble in acetone, in alcohol, in ether, in ethyl acetate, in isopropyl alcohol, in methanol, and in methylene chloride; soluble in toluene and in diisopropyl ether; practically insoluble in hexanes.

Dinoprost Tromethamine: White to off-white, crystalline powder. Very soluble in water; freely soluble in dimethylformamide; soluble in methanol; slightly soluble in chloroform.

Dioxybenzone: Yellow powder. Freely soluble in alcohol and in toluene; practically insoluble in water.

Diphenhydramine Hydrochloride: White, odorless, crystalline powder. Slowly darkens on exposure to light. Its solutions are practically neutral to litmus. Freely soluble in water, in alcohol, and in chloroform; sparingly soluble in acetone; very slightly soluble in benzene and in ether.

Diphenoxylate Hydrochloride: White, odorless, crystalline powder. Its saturated solution has a pH of about 3.3. Freely soluble in chloroform; soluble in methanol; sparingly soluble in alcohol and in acetone; slightly soluble in water and in isopropanol; practically insoluble in ether and in solvent hexane.

Diphtheria and Tetanus Toxoids Adsorbed: Turbid, and white, slightly gray, or slightly pink suspension, free from evident clumps after shaking.

Dipivefrin Hydrochloride: White, crystalline powder or small crystals, having a faint odor. Very soluble in water.

Dipyridamole: Intensely yellow, crystalline powder or needles. Very soluble in methanol, in alcohol, and in chloroform; slightly soluble in water; very slightly soluble in acetone and in ethyl acetate.

Dirithromycin: White or practically white powder. Very soluble in methanol and in methylene chloride; very slightly soluble in water.

Disopyramide Phosphate: White or practically white, odorless powder. Melts at about 205°, with decomposition. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Disulfiram: White to off-white, odorless, crystalline powder. Soluble in acetone, in alcohol, in carbon disulfide, and in chloroform; very slightly soluble in water.

Divalproex Sodium: White to off-white powder. Very soluble in chloroform; freely soluble in methanol and in ethyl ether; soluble in acetone; practically insoluble in acetonitrile.

Dobutamine Hydrochloride: White to practically white, crystalline powder. Soluble in alcohol and in pyridine; sparingly soluble in water and in methanol.

Docetaxel: White or almost white, crystalline powder. Freely soluble in acetone; soluble in methanol; practically insoluble in water.

Docusate Calcium: White, amorphous solid, having the characteristic odor of octyl alcohol. It is free of the odor of other solvents. Very soluble in alcohol, in polyethylene glycol 400, and in corn oil; very slightly soluble in water.

Docusate Potassium: White, amorphous solid, having a characteristic odor suggestive of octyl alcohol. Very soluble

in solvent hexane; soluble in alcohol and in glycerin; sparingly soluble in water.

Docusate Sodium: White, wax-like, plastic solid, having a characteristic odor suggestive of octyl alcohol, but no odor of other solvents. Very soluble in solvent hexane; freely soluble in alcohol and in glycerin; sparingly soluble in water. *NF category:* Wetting and/or solubilizing agent.

Dofetilide: White to off-white powder. Soluble in 0.1 N sodium hydroxide, in acetone, and in 0.1 N hydrochloric acid; very slightly soluble in water and in isopropyl alcohol.

Dolasetron Mesylate: White to off-white powder. Freely soluble in water and in propylene glycol; slightly soluble in alcohol and in saline TS.

Donepezil Hydrochloride: White crystalline powder. Freely soluble in chloroform; soluble in water and glacial acetic acid; slightly soluble in alcohol and acetonitrile; practically insoluble in ethyl acetate and *n*-hexane.

Dopamine Hydrochloride: White to off-white, crystalline powder. May have a slight odor of hydrochloric acid. Melts at about 240°, with decomposition. Freely soluble in water and in aqueous solutions of alkali hydroxides; soluble in methanol; insoluble in ether and in chloroform.

Dorzolamide Hydrochloride: White to off-white, crystalline powder. Soluble in water.

Doxapram Hydrochloride: White to off-white, odorless, crystalline powder. Melts at about 220°. Soluble in water and in chloroform; sparingly soluble in alcohol; practically insoluble in ether.

Doxazosin Mesylate: White to tan-colored powder. Freely soluble in formic acid; very slightly soluble in methanol and in water.

Doxorubicin Hydrochloride: Red-orange, hygroscopic, crystalline or amorphous powder. Soluble in water, in isotonic sodium chloride solution, and in methanol; practically insoluble in chloroform, in ether, and in other organic solvents.

Doxycycline: Yellow, crystalline powder. Freely soluble in dilute acid and in alkali hydroxide solutions; very slightly soluble in alcohol and in water; practically insoluble in chloroform and in ether.

Doxycycline Hyclate: Yellow, crystalline powder. Soluble in water and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Doxylamine Succinate: White or creamy white powder, having a characteristic odor. Very soluble in water and in alcohol; freely soluble in chloroform; very slightly soluble in ether and in benzene.

Dronabinol: Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Insoluble in water.

Droperidol: White to light tan, amorphous or microcrystalline powder. Freely soluble in chloroform; slightly soluble in alcohol and in ether; practically insoluble in water. Melts at about 145°.

Drospirenone: White to off-white powder. Freely soluble in methylene chloride; soluble in acetone and in methanol; sparingly soluble in ethyl acetate and in alcohol; practically insoluble in hexane and in water.

Duloxetine Hydrochloride: White to brownish-white solid. Slightly soluble in water.

Absorbable Dusting Powder: White, odorless powder.

Dyclonine Hydrochloride: White crystals or white crystalline powder, which may have a slight odor. Exhibits local anesthetic properties when placed upon the tongue. Soluble in water, in acetone, in alcohol, and in chloroform.

Hydrogesterone: White to pale yellow, crystalline powder. Sparingly soluble in alcohol; practically insoluble in water.

Dyphylline: White, odorless, extremely bitter, amorphous or crystalline solid. Freely soluble in water; sparingly soluble in alcohol and in chloroform; practically insoluble in ether.

Ecamsule Solution: Clear yellow liquid.

Echothiophate Iodide: White, crystalline, hygroscopic solid having a slight mercaptan-like odor. Its solutions have a pH of about 4. Freely soluble in water and in methanol; soluble in dehydrated alcohol; practically insoluble in other organic solvents.

Echothiophate Iodide for Ophthalmic Solution: White, amorphous powder.

Econazole Nitrate: White or practically white, crystalline powder, having not more than a slight odor. Soluble in methanol; sparingly soluble in chloroform; slightly soluble in alcohol; very slightly soluble in water and in ether.

Edetate Calcium Disodium: White, crystalline granules or white, crystalline powder. Is odorless, is slightly hygroscopic, and has a faint, saline taste. Is stable in air. Freely soluble in water. *NF category:* Chelating agent; complexing agent.

Edetate Disodium: White, crystalline powder. Soluble in water. *NF category:* Chelating agent; complexing agent.

Edetic Acid: White, crystalline powder. Melts above 220°, with decomposition. Soluble in solutions of alkali hydroxides; very slightly soluble in water. *NF category:* Chelating agent; complexing agent.

Edrophonium Chloride: White, odorless, crystalline powder. Its solution (1 in 10) is practically colorless. Very soluble in water; freely soluble in alcohol; insoluble in chloroform and in ether.

Efavirenz: White to slightly pink crystalline powder. Soluble in methanol; practically insoluble in water.

Emedastine Fumarate: White to faintly yellow, crystalline powder. Soluble in water.

Emetine Hydrochloride: White or very slightly yellowish, odorless, crystalline powder. Is affected by light. Freely soluble in water and in alcohol.

Enalapril Maleate: Off-white, crystalline powder. Melts at about 144°. Freely soluble in methanol and in dimethylformamide; soluble in alcohol; sparingly soluble in water; slightly soluble in semipolar organic solvents; practically insoluble in nonpolar organic solvents.

Enalaprilat: White to nearly white, hygroscopic, crystalline powder. Sparingly soluble in methanol and in dimethylformamide; slightly soluble in water and in isopropyl alcohol; very slightly soluble in acetone, in alcohol, and in hexane; practically insoluble in acetonitrile and in chloroform.

Enflurane: Clear, colorless, stable, volatile liquid, having a mild, sweet odor. Is nonflammable. Slightly soluble in water. Miscible with organic solvents, with fats, and with oils.

Enrofloxacin: Pale yellow to light yellow crystalline powder. Very slightly soluble in water at pH 7.

Entacapone: Greenish yellow to yellow powder. Sparingly soluble in acetone and in methanol; slightly soluble in ethanol, chloroform, isopropanol, and ether; very slightly soluble in toluene; practically insoluble in water.

Ephedrine: Unctuous, practically colorless solid or white crystals or granules. Gradually decomposes on exposure to light. Melts between 33° and 40°, the variability in the melting point being the result of differences in the moisture content, anhydrous Ephedrine having a lower melting point than the hemihydrate of Ephedrine. Its solutions are alkaline to litmus. Soluble in water, in alcohol, in chloroform, and in ether; sparingly and slowly soluble in mineral oil, the solution becoming turbid if the Ephedrine contains more than about 1% of water.

Ephedrine Hydrochloride: Fine, white, odorless crystals or powder. Is affected by light. Freely soluble in water; soluble in alcohol; insoluble in ether.

Ephedrine Sulfate: Fine, white, odorless crystals or powder. Darkens on exposure to light. Freely soluble in water; sparingly soluble in alcohol.

Ephedrine Sulfate Nasal Solution: Clear, colorless solution. Is neutral or slightly acid to litmus.

Epinephrine: White to practically white, odorless, microcrystalline powder or granules, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonia water or alkali carbonates. Its solutions are alkaline to litmus. Very slightly soluble in water and in alcohol; insoluble in ether, in chloroform, and in fixed and volatile oils.

Epinephrine Injection: Practically colorless, slightly acid liquid. Gradually turns dark on exposure to light and air.

Epinephrine Inhalation Solution: Practically colorless, slightly acid liquid. Gradually turns dark on exposure to light and air.

Epinephrine Nasal Solution: Nearly colorless, slightly acid liquid. Gradually turns dark on exposure to light and air.

Epinephrine Ophthalmic Solution: Colorless to faint yellow solution. Gradually turns dark on exposure to light and air.

Epinephrine Bitartrate: White, or grayish-white or light brownish-gray, odorless, crystalline powder. Slowly darkens on exposure to air and light. Its solutions are acid to litmus, having a pH of about 3.5. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Epinephrine Bitartrate for Ophthalmic Solution: White to off-white solid.

Epinephryl Borate Ophthalmic Solution: Clear, pale yellow liquid, gradually darkening on exposure to light and air.

Epirubicin Hydrochloride: Orange-red powder. Soluble in water and in methanol; slightly soluble in anhydrous ethanol; practically insoluble in acetone.

Eprinomectin: White to off-white powder. Insoluble in cold water.

Ergocalciferol: White, odorless crystals. Is affected by air and by light. Soluble in alcohol, in chloroform, in ether, and in fatty oils; insoluble in water.

Ergocalciferol Oral Solution: Clear liquid having the characteristics of the solvent used in preparing the Solution.

Ergoloid Mesylates: White to off-white, microcrystalline or amorphous, practically odorless powder. Soluble in methanol and in alcohol; sparingly soluble in acetone; slightly soluble in water.

Ergonovine Maleate: White to grayish-white or faintly yellow, odorless, microcrystalline powder. Darkens with age and on exposure to light. Sparingly soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform.

Ergotamine Tartrate: Colorless crystals or white to yellowish-white, crystalline powder. Is odorless. Melts at about 180°, with decomposition. One g dissolves in about 3200 mL of water; in the presence of a slight excess of tartaric acid 1 g dissolves in about 500 mL of water. Slightly soluble in alcohol.

Erythorbic Acid: White or slightly yellow crystals or powder. It gradually darkens when exposed to light. In the dry state, it is reasonably stable in air, but in solution, it rapidly deteriorates in the presence of air. It melts between 164° and 171° with decomposition. One g is soluble in about 2.5 mL of water and in about 20 mL of alcohol. Slightly soluble in glycerin. *NF category:* Antimicrobial preservative; antioxidant.

Erythritol: White or almost white, crystalline powder or free-flowing granules. It is stable to heat and is nonhygroscopic. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Humectant; sweetening agent.

Erythromycin: White or slightly yellow, crystalline powder. Is odorless or practically odorless. Soluble in alcohol, in chloroform, and in ether; slightly soluble in water.

Erythromycin Estolate: White, crystalline powder. Is odorless or practically odorless, and is practically tasteless. Soluble in alcohol, in acetone, and in chloroform; practically insoluble in water.

Erythromycin Ethylsuccinate: White or slightly yellow crystalline powder. Is odorless or practically odorless, and is practically tasteless. Freely soluble in alcohol, in chloroform, and in polyethylene glycol 400; very slightly soluble in water.

Erythromycin Gluceptate: Colorless to white crystals. Slightly hygroscopic. Freely soluble in water, in alcohol, in methanol, in dioxane, and in propylene glycol; slightly soluble in acetone and in chloroform; practically insoluble in ether, in carbon tetrachloride, in benzene, and in toluene.

Erythromycin Lactobionate for Injection: White or slightly yellow crystals or powder, having a faint odor. Its solution (1 in 20) is neutral or slightly alkaline. Freely soluble in water, in alcohol, and in methanol; slightly soluble in acetone and in chloroform; practically insoluble in ether.

Erythromycin Stearate: White or slightly yellow crystals or powder. Is odorless or may have a slight, earthy odor, and has a slightly bitter taste. Soluble in alcohol, in chloroform, in methanol, and in ether; practically insoluble in water.

Esmolol Hydrochloride: White to off-white crystalline powder. Very soluble in water; freely soluble in alcohol.

Escitalopram Oxalate: Fine, white to slightly yellow powder. Freely soluble in methanol and in dimethyl sulfoxide; sparingly soluble in water and in alcohol; very slightly soluble in ethyl acetate and in isopropyl alcohol; insoluble in heptane.

Esomeprazole Magnesium: White to slightly colored powder. Soluble in methanol; slightly soluble in water; practically insoluble in heptane.

Estazolam: White to pale yellowish-white crystal. Soluble in methanol and in acetic anhydride; sparingly soluble in ethanol; practically insoluble in water and in ether.

Estradiol: White or creamy white, small crystals or crystalline powder. Is odorless, and is stable in air. Is hygroscopic. Soluble in alcohol, in acetone, in dioxane, in chloroform, and in solutions of fixed alkali hydroxides; sparingly soluble in vegetable oils; practically insoluble in water.

Estradiol Benzoate: White to off-white, crystalline powder. Soluble in alcohol and in acetone; slightly soluble in diethyl ether; insoluble in water.

Estradiol Cypionate: White to practically white, crystalline powder. Is odorless or has a slight odor. Soluble in alcohol, in acetone, in chloroform, and in dioxane; sparingly soluble in vegetable oils; insoluble in water.

Estradiol Valerate: White, crystalline powder. Is usually odorless but may have a faint, fatty odor. Soluble in castor oil, in methanol, in benzyl benzoate, and in dioxane; sparingly soluble in sesame oil and in peanut oil; practically insoluble in water.

Estriol: White to practically white, odorless, crystalline powder. Melts at about 280°. Soluble in acetone, in chloroform, in dioxane, in ether, and in vegetable oils; sparingly soluble in alcohol; insoluble in water.

Conjugated Estrogens: Conjugated Estrogens obtained from natural sources is a buff-colored, amorphous powder, odorless or having a slight, characteristic odor. The synthetic form is a white to light buff, crystalline or amorphous powder, odorless or having a slight odor.

Synthetic Conjugated Estrogens: A white to light buff, crystalline or amorphous powder that is odorless or has a slight odor.

Esterified Estrogens: White or buff-colored, amorphous powder, odorless or having a slight, characteristic odor.

Estrone: Small, white crystals or white to creamy white, crystalline powder. Is odorless, and is stable in air. Melts at about 260°. Soluble in alcohol, in acetone, in dioxane, and in vegetable oils; slightly soluble in solutions of fixed alkali hydroxides; practically insoluble in water.

Estropipate: White to yellowish-white, fine, crystalline powder. Is odorless, or may have a slight odor. Melts at about 190° to a light brown, viscous liquid, which solidifies on further heating and finally melts at about 245°, with decomposition. Soluble in warm water; very slightly soluble in water, in alcohol, in chloroform, and in ether.

Ethacrynic Acid: White or practically white, odorless or practically odorless, crystalline powder. Freely soluble in alcohol, in chloroform, and in ether; very slightly soluble in water.

Ethambutol Hydrochloride: White, crystalline powder. Freely soluble in water; soluble in alcohol and in methanol; slightly soluble in ether and in chloroform.

Ethchlorvynol: Colorless to yellow, slightly viscous liquid, having a characteristic pungent odor. Darkens on exposure to light and air. Immiscible with water; miscible with most organic solvents.

Ether: Colorless, mobile, volatile liquid, having a characteristic sweet, pungent odor. Is slowly oxidized by the action of air and light, with the formation of peroxides. It boils at about 35°. Soluble in water and in hydrochloric acid. Miscible with alcohol, with benzene, with chloroform, with solvent hexane, with methylene chloride, and with fixed and volatile oils.

Ethinyl Estradiol: White to creamy white, odorless, crystalline powder. Soluble in alcohol, in chloroform, in ether, in vegetable oils, and in solutions of fixed alkali hydroxides; insoluble in water.

Ethiodized Oil Injection: Straw-colored to amber-colored, oily liquid. It may possess an alliaceous odor. Soluble in acetone, in chloroform, in ether, and in solvent hexane; insoluble in water.

Ethionamide: Bright yellow powder, having a faint to moderate sulfide-like odor. Soluble in methanol; sparingly soluble in alcohol and in propylene glycol; slightly soluble in water, in chloroform, and in ether.

Ethopabate: White to pinkish-white, odorless or practically odorless powder. Soluble in acetonitrile, in acetone, in dehydrated alcohol, and in methanol; sparingly soluble in isopropyl alcohol, in dioxane, in ethyl acetate, and in methylene chloride; slightly soluble in ether; very slightly soluble in water.

Ethosuximide: White to off-white, crystalline powder or waxy solid, having a characteristic odor. Freely soluble in water and in chloroform; very soluble in alcohol and in ether; very slightly soluble in solvent hexane.

Ethotoin: White, crystalline powder. Freely soluble in dehydrated alcohol and in chloroform; soluble in ether; insoluble in water.

Ethyl Acetate: Transparent, colorless liquid, having a fragrant, refreshing, slightly acetous odor, and a peculiar, acetous, burning taste. Soluble in water. Miscible with alcohol, with ether, with fixed oils, and with volatile oils. *NF category:* Flavors and perfumes; solvent.

Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion: Milky-white liquid of low viscosity with a faint, characteristic odor. It is miscible with water in any proportion; the milky-white appearance is retained. A clear or slightly opalescent, viscous solution is obtained on mixing one part with five parts of acetone, alcohol, or isopropyl alcohol; the polymer substance first precipitates, but then

dissolves in the excess organic solvent. When mixed with 1 N sodium hydroxide in a ratio of 1:2, the dispersion does not dissolve; the milky-white appearance is retained. *NF category:* Coating agent; polymer membrane; tablet binder.

Ethyl Chloride: Colorless, mobile, very volatile liquid at low temperatures or under pressure, having a characteristic, ethereal odor. It boils between 12° and 13°, and its specific gravity at 0° is about 0.921. When liberated at room temperature from its sealed container, it vaporizes immediately. It burns with a smoky, greenish flame, producing hydrogen chloride. Freely soluble in alcohol and in ether; slightly soluble in water.

Ethyl Oleate: Mobile, practically colorless liquid, having an agreeable taste. Insoluble in water. Miscible with vegetable oils, with mineral oil, with alcohol, and with most organic solvents. *NF category:* Vehicle (oleaginous).

Ethyl Maltol: White, crystalline powder having a cotton-candy odor and a sweet, fruitlike flavor in dilute solution. One g dissolves in about 55 mL of water, 10 mL of alcohol, 17 mL of propylene glycol, and 5 mL of chloroform. It melts at about 90°. *NF category:* Vehicle (flavored and/or sweetened).

Ethyl Vanillin: Fine, white or slightly yellowish crystals. Its taste and odor are similar to the taste and odor of vanillin. Is affected by light. Its solutions are acid to litmus. Freely soluble in alcohol, in chloroform, in ether, and in solutions of alkali hydroxides; sparingly soluble in water at 50°. *NF category:* Flavors and perfumes.

Ethylcellulose: Free-flowing, white to light tan powder. It forms films that have a refractive index of about 1.47. Its aqueous suspensions are neutral to litmus. Ethylcellulose containing less than 46.5% of ethoxy groups is freely soluble in tetrahydrofuran, in methyl acetate, in chloroform, and in mixtures of aromatic hydrocarbons with alcohol; Ethylcellulose containing not less than 46.5% of ethoxy groups is freely soluble in alcohol, in methanol, in toluene, in chloroform, and in ethyl acetate; insoluble in water, in glycerin, and in propylene glycol. *NF category:* Coating agent; tablet binder.

Change to read:

Ethylcellulose Dispersion Type B: Off-white and slightly viscous liquid. Soluble in alcohol, in methyl alcohol, in tetrahydrofuran, and in ethyl acetate; insoluble in water and in chloroform. (ERR 1-Oct-2012) *NF category:* Coating agent; film-forming agent.

Ethylenediamine: Clear, colorless or only slightly yellow liquid, having an ammonia-like odor and a strong alkaline reaction. Miscible with water and with alcohol.

Ethylene Glycol Stearates: White or almost white, waxy solid. Soluble in acetone and in hot alcohol; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Ethylene Glycol and Vinyl Alcohol Graft Copolymer: White or slightly yellowish powder. Very soluble in water; practically insoluble in anhydrous alcohol, and in acetone. It dissolves in dilute acids and dilute solutions of alkali hydroxides. *NF category:* Coating agent; tablet binder.

Ethylparaben: Small, colorless crystals or white powder. Freely soluble in acetone, in alcohol, in ether, and in propylene glycol; slightly soluble in water and in glycerin. *NF category:* Antimicrobial preservative.

Ethynodiol Diacetate: White, odorless, crystalline powder. Is stable in air. Very soluble in chloroform; freely soluble in ether; soluble in alcohol; sparingly soluble in fixed oils; insoluble in water.

Etidronate Disodium: White powder, which may contain lumps. Freely soluble in water; practically insoluble in alcohol.

Etomidate: White or almost white powder. Freely soluble in alcohol and in methylene chloride; very slightly soluble in water.

Etoposide: Fine, white to off-white, crystalline powder. Sparingly soluble in methanol; slightly soluble in alcohol, in chloroform, in ethyl acetate, and in methylene chloride; very slightly soluble in water.

Eugenol: Colorless or pale yellow liquid, having a strongly aromatic odor of clove and a pungent, spicy taste. Upon exposure to air, it darkens and thickens. Is optically inactive. Slightly soluble in water. Miscible with alcohol, with chloroform, with ether, and with fixed oils.

Add the following:

• **Famciclovir:** A white to pale yellow solid. Freely soluble in methanol and in acetone; sparingly soluble in ethanol and in isopropyl alcohol. (RB 1-Feb-2013)

Famotidine: White to pale yellowish-white, crystalline powder. Is sensitive to light. Freely soluble in dimethylformamide and in glacial acetic acid; slightly soluble in methanol; very slightly soluble in water; practically insoluble in acetone, in alcohol, in chloroform, in ether, and in ethyl acetate.

Hard Fat: White mass; almost odorless and free from rancid odor; greasy to the touch. On warming, melts to give a colorless or slightly yellowish liquid. When the molten material is shaken with an equal quantity of hot water, a white emulsion is formed. Freely soluble in ether; slightly soluble in alcohol; practically insoluble in water. *NF category:* Stiffening agent; suppository base.

Felbamate: White to off-white powder. Freely soluble in dimethyl sulfoxide; sparingly soluble in methanol; slightly soluble in acetonitrile; very slightly soluble in water.

Felodipine: Light yellow to yellow, crystalline powder. Freely soluble in acetone and in methanol; very slightly soluble in heptane; insoluble in water.

Fenbendazole: White to off-white powder. Sparingly soluble in dimethylformamide; very slightly soluble in methanol; practically insoluble in water.

Fenofibrate: White or almost white, crystalline powder. Very soluble in methylene chloride; slightly soluble in alcohol; practically insoluble in water.

Fenoldopam Mesylate: White to off-white powder. Soluble in water.

Fenoprofen Calcium: White, crystalline powder. Slightly soluble in *n*-hexanol, in methanol, and in water; practically insoluble in chloroform.

Fentanyl Citrate: White, crystalline powder or white, glistening crystals. Melts at about 150°, with decomposition. Soluble in methanol; sparingly soluble in water; slightly soluble in chloroform.

Ferric Oxide: Powder exhibiting two basic colors (red and yellow), or other shades produced on blending the basic colors. Insoluble in water and in organic solvents; dissolves in hydrochloric acid upon warming, a small amount of insoluble residue usually remaining. *NF category:* Color.

Ferric Subsulfate Solution: Reddish-brown liquid, odorless or nearly so. Acid to litmus, and is affected by light. Specific gravity is about 1.548.

Ferric Sulfate: Grayish-white or yellowish powder or fawn-colored pearls. Hygroscopic. Slightly soluble in water and in ethanol (96%); practically insoluble in acetone and in ethyl acetate. Hydrolyzes slowly in aqueous solution.

Ferrosulfate: Black powder. Dissolves in hydrochloric acid upon warming, a small amount of insoluble residue usually remaining; insoluble in water and in organic solvents. *NF category:* Color.

Ferrous Fumarate: Reddish-orange to red-brown, odorless powder. May contain soft lumps that produce a

yellow streak when crushed. Slightly soluble in water; very slightly soluble in alcohol. Its solubility in dilute hydrochloric acid is limited by the separation of fumaric acid.

Ferrous Gluconate: Yellowish-gray or pale greenish-yellow, fine powder or granules, having a slight odor resembling that of burned sugar. Its solution (1 in 20) is acid to litmus. Soluble in water, with slight heating; practically insoluble in alcohol.

Ferrous Sulfate: Pale, bluish-green crystals or granules. Is odorless and is efflorescent in dry air. Oxidizes readily in moist air to form brownish yellow basic ferric sulfate. Its solution (1 in 10) is acid to litmus, having a pH of about 3.7. Very soluble in boiling water; freely soluble in water; insoluble in alcohol.

Dried Ferrous Sulfate: Grayish-white to buff-colored powder, consisting primarily of $\text{FeSO}_4 \cdot \text{H}_2\text{O}$ with varying amounts of $\text{FeSO}_4 \cdot 4\text{H}_2\text{O}$. Slowly soluble in water; insoluble in alcohol.

Ferumoxides Injection: Black to reddish-brown, aqueous colloid. It is stable for 24 hours after dilution.

Add the following:

• **Fexofenadine Hydrochloride:** White to off-white powder. Freely soluble in methanol; slightly soluble in water; very slightly soluble in acetone. (USP36)

Finasteride: White to off-white, crystalline solid. Melts at about 257°. Freely soluble in chloroform and in alcohol; very slightly soluble in water.

Fish Oil Containing Omega-3 Acids: Pale yellow liquid. Very soluble in acetone and in heptane; slightly soluble in anhydrous alcohol; practically insoluble in water.

Flavoxate Hydrochloride: White or almost white, crystalline powder. Slightly soluble in alcohol, in water, and in methylene chloride.

Flecainide Acetate: White to slightly off-white, crystalline powder. Freely soluble in alcohol; soluble in water. pK_a is 9.3.

Fluconazole: White or almost white, crystalline powder. Freely soluble in methanol; soluble in alcohol and in acetone; sparingly soluble in isopropanol and in chloroform; slightly soluble in water; very slightly soluble in toluene.

Flucytosine: White to off-white, crystalline powder. Is odorless or has a slight odor. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Fludarabine Phosphate: White to off-white, crystalline, hygroscopic powder. Freely soluble in dimethylformamide; slightly soluble in water and in 0.1 M hydrochloric acid; practically insoluble in ethanol.

Fludrocortisone Acetate: White to pale yellow crystals or crystalline powder. Is odorless or practically odorless. Is hygroscopic. Sparingly soluble in alcohol and in chloroform; slightly soluble in ether; insoluble in water.

Flumazenil: White to off-white powder. Slightly soluble in acidic aqueous solutions; practically insoluble in water.

Flumethasone Pivalate: White to off-white, crystalline powder. Slightly soluble in methanol; very slightly soluble in chloroform and in methylene chloride; insoluble in water.

Flunisolide: White to creamy-white, crystalline powder. Melts at about 245°, with decomposition. Soluble in acetone; sparingly soluble in chloroform; slightly soluble in methanol; practically insoluble in water.

Flunixin Meglumine: White to off-white crystalline powder. Soluble in water, in alcohol, and in methanol; practically insoluble in ethyl acetate.

Fluocinolone Acetonide: White or practically white, odorless, crystalline powder. Is stable in air. Melts at about 270°, with decomposition. Soluble in methanol; slightly soluble in ether and in chloroform; insoluble in water.

Fluocinonide: White to cream-colored, crystalline powder, having not more than a slight odor. Sparingly soluble in acetone and in chloroform; slightly soluble in alcohol, in methanol, and in dioxane; very slightly soluble in ether; practically insoluble in water.

Fluorescein: Yellowish-red to red, odorless powder. Soluble in dilute alkali hydroxides; insoluble in water.

Fluorescein Sodium: Orange-red, hygroscopic, odorless powder. Freely soluble in water; sparingly soluble in alcohol.

Fluorescein Sodium Ophthalmic Strip: Each Strip is a dry, white piece of paper, one end of which is rounded and is uniformly orange-red in color because of the fluorescein sodium impregnated in the paper.

Fluorometholone: White to yellowish-white, odorless, crystalline powder. Melts at about 280°, with some decomposition. Slightly soluble in water; slightly soluble in chloroform and in ether; practically insoluble in water.

Fluorouracil: White to practically white, practically odorless, crystalline powder. Decomposes at about 282°. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Fluoxetine Hydrochloride: White to off-white crystalline powder. Freely soluble in alcohol and in methanol; sparingly soluble in water and in dichloromethane; practically insoluble in ether.

Fluoxymesterone: White or practically white, odorless, crystalline powder. Melts at about 240°, with some decomposition. Sparingly soluble in alcohol; slightly soluble in chloroform; practically insoluble in water.

Fluphenazine Enanthate: Pale yellow to yellow-orange, clear to slightly turbid, viscous liquid, having a characteristic odor. Is unstable in strong light, but stable to air at room temperature. Freely soluble in alcohol, in chloroform, and in ether; insoluble in water.

Fluphenazine Hydrochloride: White or nearly white, odorless, crystalline powder. Melts, within a range of 5°, at a temperature above 225°. Freely soluble in water; slightly soluble in acetone, in alcohol, and in chloroform; practically insoluble in benzene and in ether.

Flurandrenolide: White to off-white, fluffy, crystalline powder. Is odorless. Freely soluble in chloroform; soluble in methanol; sparingly soluble in alcohol; practically insoluble in water and in ether.

Flurazepam Hydrochloride: Off-white to yellow, crystalline powder. Is odorless, or has a slight odor, and its solutions are acid to litmus. Melts at about 212°, with decomposition. Freely soluble in water and in alcohol; slightly soluble in isopropyl alcohol and in chloroform.

Flurbiprofen: White, crystalline powder. Freely soluble in acetone, in dehydrated alcohol, in ether, and in methanol; soluble in acetonitrile; practically insoluble in water. Optically inactive (1 in 50 solution in dehydrated alcohol).

Flutamide: Pale yellow, crystalline powder. Freely soluble in acetone, in ethyl acetate, and in methanol; soluble in chloroform and in ether; practically insoluble in mineral oil, in petroleum ether, and in water.

Fluticasone Propionate (micronized): Fine, white powder.

Fluvastatin Sodium: White to pale yellow, brownish-pale yellow, or reddish-pale yellow, hygroscopic powder. Soluble in alcohol, in methanol, and in water.

Fluvoxamine Maleate: White to off-white, crystalline powder. Freely soluble in alcohol and in chloroform; sparingly soluble in water; and practically insoluble in diethyl ether.

Folic Acid: Yellow, yellow-brownish, or yellowish-orange, odorless, crystalline powder. It readily dissolves in dilute solutions of alkali hydroxides and carbonates. Soluble in hot, 3 N hydrochloric acid, in hot, 2 N sulfuric acid, in hydrochloric acid, and in sulfuric acid, yielding very pale yellow

solutions; very slightly soluble in water; insoluble in alcohol, in acetone, in chloroform, and in ether.

Folic Acid Injection: Clear, yellow to orange-yellow, alkaline liquid.

Formaldehyde Solution: Clear, colorless or practically colorless liquid, having a pungent odor. The vapor from it irritates the mucous membrane of the throat and nose. On long standing, especially in the cold, it may become cloudy because of the separation of paraformaldehyde. This cloudiness disappears when the solution is warmed. Miscible with water and with alcohol.

Formoterol Fumarate Dihydrate: White or almost white or slightly yellow powder. Freely soluble in dimethyl sulfoxide and in acetic acid; soluble in methanol; slightly soluble in water and in 2-propanol; practically insoluble in acetonitrile and in diethyl ether.

Foscarnet Sodium: White to almost white, crystalline powder. Soluble in water; practically insoluble in alcohol.

Fosphenytoin Sodium: White to pale yellow solid. Freely soluble in water.

Fructose: Colorless crystals or as a white, crystalline powder. Is odorless, and has a sweet taste. Freely soluble in water; soluble in alcohol and in methanol. *NF category:* Sweetening agent; tablet and/or capsule diluent.

Basic Fuchsin: Dark green powder or greenish glistening crystalline fragments, having a bronze-like luster and not more than a faint odor. Soluble in water, in alcohol, and in amyl alcohol; insoluble in ether.

Fulvestrant: White powder. Freely soluble in alcohol.

Fumaric Acid: White, odorless granules or crystalline powder. Soluble in alcohol; slightly soluble in water and in ether; very slightly soluble in chloroform. *NF category:* Acidifying agent.

Furazolidone: Yellow, odorless, crystalline powder. Is tasteless at first, then a bitter aftertaste develops. Practically insoluble in water, in alcohol, and in carbon tetrachloride.

Furosemide: White to slightly yellow, odorless, crystalline powder. Freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; soluble in methanol; sparingly soluble in alcohol; slightly soluble in ether; very slightly soluble in chloroform; practically insoluble in water.

Furosemide Injection: Clear, colorless solution.

Gabapentin: White to off-white, crystalline solid. Freely soluble in water and in alkaline and acidic solutions.

Gadodiamide: White, odorless powder. Freely soluble in water and in methanol; soluble in ethyl alcohol; slightly soluble in acetone and in chloroform.

Gadoteridol: White to off-white, crystalline, odorless powder. Freely soluble in water and in methyl alcohol; soluble in isopropyl alcohol. Melts at about 300°.

Gadoversetamide: White, odorless powder. Freely soluble in water.

Galactose: A white, crystalline or finely granulated powder. Soluble in water; very slightly soluble in alcohol. *NF category:* Sweetening agent.

Galantamine Hydrobromide: White to almost white powder. Soluble in 0.1 N sodium hydroxide; sparingly soluble in water; very slightly soluble in alcohol; insoluble in *n*-propanol.

Gallamine Triethiodide: White, odorless, amorphous powder. Is hygroscopic. Very soluble in water; sparingly soluble in alcohol; very slightly soluble in chloroform.

Gamma Cyclodextrin: White or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; very slightly soluble in alcohol. *NF category:* Sequestering agent; emulsifying and/or solubilizing agent.

Ganciclovir: White to off-white, crystalline powder.

Ganciclovir for Injection: White to off-white powder. Soluble in water.

Petrolatum Gauze: The petrolatum recovered by draining in the Assay is a white or faintly yellowish, unctuous mass, transparent in thin layers even after cooling to 0°.

Gelatin: Sheets, flakes, or shreds, or coarse to fine powder. Is faintly yellow or amber in color, the color varying in depth according to the particle size. Has a slight, characteristic bouillon-like odor in solution. Is stable in air when dry, but is subject to microbic decomposition when moist or in solution. Gelatin has any suitable strength that is designated by Bloom Gelometer number (see *Gel Strength of Gelatin* (1081)). Type A Gelatin exhibits an isoelectric point between pH 7 and pH 9, and Type B Gelatin exhibits an isoelectric point between pH 4.7 and pH 5.2. Soluble in hot water, in 6 N acetic acid, and in a hot mixture of glycerin and water; insoluble in cold water, but swells and softens when immersed in it, gradually absorbing from 5 to 10 times its own weight of water, in alcohol, in chloroform, in ether, and in fixed and volatile oils. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Absorbable Gelatin Film: Light amber, transparent, pliable film which becomes rubbery when moistened. Insoluble in water.

Absorbable Gelatin Sponge: Light, nearly white, nonelastic, tough, porous, hydrophilic solid. Insoluble in water.

Gellan Gum: Off-white powder. Soluble in hot or in cold deionized water. *NF category:* Suspending and/or viscosity-increasing agent.

Gemcitabine Hydrochloride: White to off-white solid. Soluble in water; slightly soluble in methanol; practically insoluble in alcohol and in polar organic solvents.

Gemfibrozil: White, waxy, crystalline solid. Soluble in alcohol, in methanol, and in chloroform; practically insoluble in water.

Gentamicin Sulfate: White to buff powder. Freely soluble in water; insoluble in alcohol, in acetone, in chloroform, in ether, and in benzene.

Gentamicin Injection: Clear, slightly yellow solution, having a faint odor.

Gentian Violet: Dark green powder or greenish, glistening pieces having a metallic luster, and having not more than a faint odor. Soluble in alcohol, in glycerin, and in chloroform; sparingly soluble in water; insoluble in ether.

Gentian Violet Cream: Dark purple, water-washable cream.

Gentian Violet Topical Solution: Purple liquid, having a slight odor of alcohol. A dilution (1 in 100), viewed downward through 1 cm of depth, is deep purple in color.

Powdered Asian Ginseng Extract: Pale yellow-brown, hygroscopic, powdery or easily pulverizable mass. Soluble in water, forming a slightly cloudy solution.

Glaze, Pharmaceutical: Denatured alcohol solution. *NF category:* Coating agent.

Glimepiride: White to almost white powder. Soluble in dimethylformamide; sparingly soluble in methylene chloride; slightly soluble in methanol; practically insoluble in water.

Glipizide: White to off-white powder. Freely soluble in dimethylformamide; soluble in 0.1 N sodium hydroxide; slightly soluble in methylene chloride.

Immune Globulin: Transparent or slightly opalescent liquid, either colorless or of a brownish color due to denatured hemoglobin. Is practically odorless. May develop a slight, granular deposit during storage.

Rh₀(D) Immune Globulin: Transparent or slightly opalescent liquid. Is practically colorless and odorless. May develop a slight, granular deposit during storage.

Glucagon: Fine, white or faintly colored, crystalline powder. Is practically odorless and tasteless. Soluble in di-

lute alkali and acid solutions; insoluble in most organic solvents.

Glucagon for Injection: White, odorless powder.

Gluconolactone: Fine, white, practically odorless, crystalline powder. Melts at about 153°, with decomposition. Freely soluble in water; sparingly soluble in alcohol; insoluble in ether.

Liquid Glucose: Colorless or yellowish, thick, syrupy liquid. Odorless or nearly odorless, and has a sweet taste. Sparingly soluble in alcohol. Miscible with water. *NF category:* Tablet binder.

L-Glutamic Acid Hydrochloride: A white, crystalline powder. 1 g dissolves in about 3 mL of water. It is almost insoluble in alcohol and in ether. Its solutions are acid to litmus. *NF category:* Flavors and perfumes.

Glutamine: White crystals or crystalline powder. Soluble in water; practically insoluble in alcohol and in ether.

Glutaral Concentrate: Clear, colorless or faintly yellow liquid, having a characteristic, irritating odor.

Glycerin: Clear, colorless, syrupy liquid, having a sweet taste. Has not more than a slight characteristic odor, which is neither harsh nor disagreeable. Is hygroscopic. Its solutions are neutral to litmus. Insoluble in chloroform, in ether, and in fixed and volatile oils. Miscible with water and with alcohol. *NF category:* Humectant; plasticizer; solvent; tonicity agent.

Glyceryl Behenate: Fine powder, having a faint odor. Melts at about 70°. Soluble in chloroform; practically insoluble in water and in alcohol.

Glyceryl Distearate: Hard, waxy mass or powder or white or almost white flakes. Soluble in methylene chloride and in tetrahydrofuran; slightly soluble in hot alcohol; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Glyceryl Monolinoleate: Amber, oily liquids that may be partially solidified at room temperature. Freely soluble in methylene chloride; soluble in tetrahydrofuran; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Glyceryl Monooleate: Amber, oily liquids that may be partially solidified at room temperature. Freely soluble in methylene chloride; soluble in tetrahydrofuran; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Glyceryl Monostearate: White to yellowish wax-like solid; or white to yellowish wax-like beads, flakes, or powder. Slight, agreeable, fatty odor and taste. Is affected by light. Dissolves in hot organic solvents such as alcohol, minerals or fixed oils, benzene, ether, and acetone. Insoluble in water, but it may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent. *NF category:* Emulsifying and/or solubilizing agent.

Add the following:

▲Glyceryl Tristearate: White, solid, microcrystalline powder. Soluble in hot alcohol, in acetone, and in chloroform; very slightly soluble in cold alcohol, in ether, and in petroleum ether; insoluble in water. *NF category:* Tablet and/or capsule lubricant; emulsifying and/or solubilizing agent. ▲NF31

Glycine: White, odorless, crystalline powder, having a sweetish taste. Its solutions are acid to litmus. Freely soluble in water; very slightly soluble in alcohol and in ether.

Glycopyrrolate: White, odorless, crystalline powder. Soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Gonadorelin Acetate: White to slightly yellowish powder. Soluble in water; sparingly soluble in methanol.

Chorionic Gonadotropin: White or practically white, amorphous powder. Freely soluble in water.

Chorionic Gonadotropin for Injection: White or practically white, amorphous solid having the characteristic appearance of substances prepared by freeze-drying.

Gramicidin: White or practically white, odorless, crystalline powder. Soluble in alcohol; insoluble in water.

Granisetron Hydrochloride: White or almost white powder. Freely soluble in water; sparingly soluble in methylene chloride; slightly soluble in methanol.

Green Soap: Soft, unctuous, yellowish-white to brownish or greenish yellow, transparent to translucent mass. Has a slight, characteristic odor, often suggesting the oil from which it was prepared. Its solution (1 in 20) is alkaline to bromothymol blue TS.

Griseofulvin: White to creamy white, odorless powder, in which particles of the order of 4 μm in diameter predominate. Soluble in acetone, in dimethylformamide, and in chloroform; sparingly soluble in alcohol; very slightly soluble in water.

Guaifenesin: White to slightly gray, crystalline powder. May have a slight characteristic odor. Soluble in water, in alcohol, in chloroform, and in propylene glycol; sparingly soluble in glycerin.

Guanabenz Acetate: White or almost white powder having not more than a slight odor. Soluble in alcohol and in propylene glycol; sparingly soluble in water and in 0.1 N hydrochloric acid.

Guanadrel Sulfate: White to off-white, crystalline powder. Melts at about 235°, with decomposition. Soluble in water; sparingly soluble in methanol; slightly soluble in alcohol and in acetone.

Guanethidine Monosulfate: White to off-white, crystalline powder. Very soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform.

Guar Gum: White to yellowish-white, practically odorless powder. Dispersible in hot or cold water, forming a colloidal solution. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder.

Gutta Percha: Lumps or blocks of variable size; externally brown or grayish-brown to grayish-white in color; internally reddish yellow or reddish gray and having a laminated or fibrous appearance. Is flexible but only slightly elastic. Has a slight, characteristic odor and a slight taste. Soluble in chloroform; partly soluble in benzene, in carbon disulfide, and in turpentine oil; insoluble in water.

Halazone: White, crystalline powder, having a characteristic chlorine-like odor. Is affected by light. Melts at about 194°, with decomposition. Soluble in glacial acetic acid; very slightly soluble in water and in chloroform. Dissolves in solutions of alkali hydroxides and carbonates with the formation of a salt.

Halazone Tablets for Solution: Soluble in water.

Halcinonide: White to off-white, odorless, crystalline powder. Soluble in acetone and in chloroform; slightly soluble in alcohol and in ethyl ether; insoluble in water and in hexanes.

Halobetasol Propionate: White to off-white powder. Freely soluble in dichloromethane and in acetone; practically insoluble in water.

Haloperidol: White to faintly yellowish, amorphous or microcrystalline powder. Its saturated solution is neutral to litmus. Soluble in chloroform; sparingly soluble in alcohol; slightly soluble in ether; practically insoluble in water.

Haloperidol Decanoate: A white or almost white powder. Very soluble in alcohol, in methanol, and in methylene chloride; practically insoluble in water.

Halothane: Colorless, mobile, nonflammable, heavy liquid, having a characteristic odor resembling that of chloroform. Its taste is sweet and produces a burning sensation.

Slightly soluble in water. Miscible with alcohol, with chloroform, with ether, and with fixed oils.

Helium: Colorless, odorless, tasteless gas, which is not combustible and does not support combustion. Very slightly soluble in water. At 0° and at a pressure of 760 mm of mercury, 1000 mL of the gas weighs about 180 mg.

Heparin Sodium: White or pale-colored, amorphous powder. Is odorless or practically so, and is hygroscopic. Soluble in water.

Hexachlorophene: White to light tan, crystalline powder. Is odorless or has only a slight, phenolic odor. Freely soluble in acetone, in alcohol, and in ether; soluble in chloroform and in dilute solutions of fixed alkali hydroxides; insoluble in water.

Hexachlorophene Liquid Soap: Clear, amber-colored liquid, having a slight, characteristic odor. Its solution (1 in 20) is clear and has an alkaline reaction.

Hexylene Glycol: Clear, colorless, viscous liquid. Absorbs moisture when exposed to moist air. Miscible with water and with many organic solvents, including alcohol, ether, chloroform, acetone, and hexanes. *NF category:* Humectant; solvent.

Histamine Phosphate: Colorless, odorless, long prismatic crystals. Is stable in air but is affected by light. Its solutions are acid to litmus. Freely soluble in water.

Histidine: White, odorless crystals, having a slightly bitter taste. Soluble in water; very slightly soluble in alcohol; insoluble in ether.

Histoplasmin: Clear, red liquid. Miscible with water.

Homatropine Hydrobromide: White crystals, or white, crystalline powder. Slowly darkens on exposure to light. Freely soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; insoluble in ether. Melts between 214° and 217°, with slight decomposition.

Homatropine Methylbromide: White, odorless powder. Slowly darkens on exposure to light. Melts at about 190°. Very soluble in water; freely soluble in alcohol and in acetone containing about 20% of water; practically insoluble in ether and in acetone.

Hydralazine Hydrochloride: White to off-white, odorless, crystalline powder. Melts at about 275°, with decomposition. Soluble in water; slightly soluble in alcohol; very slightly soluble in ether.

Hydrochloric Acid: Colorless, fuming liquid having a pungent odor. It ceases to fume when it is diluted with 2 volumes of water. Specific gravity is about 1.18. *NF category:* Acidifying agent.

Diluted Hydrochloric Acid: Colorless, odorless liquid. Specific gravity is about 1.05. *NF category:* Acidifying agent.

Hydrochlorothiazide: White, or practically white, practically odorless, crystalline powder. Freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; very slightly soluble in water; sparingly soluble in methanol; insoluble in ether, in chloroform, and in dilute mineral acids.

Hydrocodone Bitartrate: Fine, white crystals or a crystalline powder. Is affected by light. Soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform.

Hydrocortisone: White to practically white, odorless, crystalline powder. Melts at about 215°, with decomposition. Sparingly soluble in acetone and in alcohol; slightly soluble in chloroform; very slightly soluble in water and in ether.

Hydrocortisone Acetate: White to practically white, odorless, crystalline powder. Melts at about 200°, with decomposition. Slightly soluble in alcohol and in chloroform; insoluble in water.

Hydrocortisone Butyrate: White to practically white, practically odorless, crystalline powder. Freely soluble in chloroform; soluble in methanol, in alcohol, and in acetone; slightly soluble in ether; practically insoluble in water.

Hydrocortisone Sodium Phosphate: White to light yellow, odorless or practically odorless, powder. Is exceedingly hygroscopic. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform, in dioxane, and in ether.

Hydrocortisone Sodium Succinate: White or nearly white, odorless, hygroscopic, amorphous solid. Very soluble in water and in alcohol; very slightly soluble in acetone; insoluble in chloroform.

Hydroflumethiazide: White to cream-colored, finely divided, odorless, crystalline powder. Freely soluble in acetone; soluble in alcohol; very slightly soluble in water.

Hydrogen Peroxide Concentrate: Clear, colorless liquid. Is acid to litmus. Slowly decomposes, and is affected by light.

Hydrogen Peroxide Solution: Clear, colorless liquid, odorless, or having an odor resembling that of ozone. Is acid to litmus and to the taste and produces a froth in the mouth. Rapidly decomposes when in contact with many oxidizing as well as reducing substances. When rapidly heated, it may decompose suddenly. Is affected by light. Specific gravity is about 1.01.

Hydromorphone Hydrochloride: Fine, white or practically white, odorless, crystalline powder. Is affected by light. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in ether.

Hydroquinone: Fine white needles. Darkens upon exposure to light and air. Freely soluble in water, in alcohol, and in ether.

Hydroxocobalamin: Dark red crystals or red crystalline powder. Is odorless, or has not more than a slight acetone odor. The anhydrous form is very hygroscopic. Sparingly soluble in water, in alcohol, and in methanol; practically insoluble in acetone, in ether, in chloroform, and in benzene.

Hydroxyamphetamine Hydrobromide: White, crystalline powder. Its solutions are slightly acid to litmus, having a pH of about 5. Freely soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether.

Hydroxychloroquine Sulfate: White or practically white, crystalline powder. Is odorless, and has a bitter taste. Its solutions have a pH of about 4.5. Exists in two forms, the usual form melting at about 240° and the other form melting at about 198°. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether.

Hydroxyethyl Cellulose: White to light tan, practically odorless and tasteless, hygroscopic powder. Soluble in hot water and in cold water, giving a colloidal solution; practically insoluble in alcohol and in most organic solvents. *NF category:* Suspending and/or viscosity-increasing agent.

Hydroxyprogesterone Caproate: White or creamy white, crystalline powder. Is odorless or has a slight odor. Soluble in ether; slightly soluble in benzene; insoluble in water.

Hydroxypropyl Betadex: White or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol. *NF category:* Sequestering agent.

Hydroxypropyl Cellulose: White to cream-colored, practically odorless and tasteless, granular solid or powder. Is hygroscopic after drying. Soluble in cold water, in alcohol, in chloroform, and in propylene glycol, giving a colloidal solution; insoluble in hot water. *NF category:* Coating agent; suspending and/or viscosity-increasing agent.

Low-Substituted Hydroxypropyl Cellulose: White to yellowish-white, practically odorless and tasteless, fibrous or granular powder. Is hygroscopic. Practically insoluble in alcohol and in ether. Dissolves in a solution of sodium hydroxide (1 in 10), and produces a viscous solution. Swells in water, in sodium carbonate TS, and in 2 N hydrochloric acid. The pH of the suspension, obtained by shaking 1.0 g with 100 mL of water, is between 5.0 and 7.5. *NF category:* Tablet binder; tablet disintegrant.

Hydroxyurea: White to off-white powder. Is somewhat hygroscopic, decomposing in the presence of moisture. Melts at a temperature exceeding 133°, with decomposition. Freely soluble in water and in hot alcohol.

Hydroxyzine Hydrochloride: White, odorless powder. Melts at about 200°, with decomposition. Very soluble in water; soluble in chloroform; slightly soluble in acetone; practically insoluble in ether.

Hydroxyzine Pamoate: Light yellow, practically odorless powder. Freely soluble in dimethylformamide; practically insoluble in water and in methanol.

Hymetellose: A white, yellowish-white or grayish-white powder or granules. Hygroscopic after drying. Dissolves in cold water, giving a colloidal solution. Insoluble in hot water, in acetone, in alcohol, in ether, and in toluene.

Hyoscyamine: White, crystalline powder. Is affected by light. Its solutions are alkaline to litmus. Freely soluble in alcohol, in chloroform, and in dilute acids; sparingly soluble in ether; slightly soluble in water and in benzene.

Hyoscyamine Hydrobromide: White, odorless crystals or crystalline powder. The pH of a solution (1 in 20) is about 5.4. Is affected by light. Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in ether.

Hyoscyamine Sulfate: White or almost white, crystalline powder or colorless needles. Is deliquescent and is affected by light. The pH of a solution (1 in 100) is about 5.3. Very soluble in water; freely soluble in alcohol; practically insoluble in ether. Melts at a temperature not less than 200°.

Hypophosphorous Acid: Colorless or slightly yellow, odorless liquid. Specific gravity is about 1.13. *NF category:* Antioxidant.

Hypromellose: White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Hypromellose 2208: White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Hypromellose 2906: White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Hypromellose 2910: White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Hypromellose Acetate Succinate: White to yellowish-white powder or pills. Odorless, or has a faint, acetic acid-like odor, and tasteless. Practically insoluble in water, in dehydrated alcohol, in xylene, and in hexane. On the addition of a mixture of dehydrated alcohol and dichloromethane (1:1) or acetone, a clear or turbid viscous liquid is produced. Dissolves in 1 N sodium hydroxide. Slightly hygroscopic. *NF category:* Coating agent; tablet binder.

Hypromellose Phthalate: White powder or granules. Is odorless and tasteless. Practically insoluble in water, in dehydrated alcohol, and in hexane. Produces a viscous solution in a mixture of methanol and dichloromethane (1:1), or in a mixture of dehydrated alcohol and acetone (1:1). Dissolves in 1 N sodium hydroxide. *NF category:* Coating agent.

Ibuprofen: White to off-white, crystalline powder, having a slight, characteristic odor. Very soluble in alcohol, in

methanol, in acetone, and in chloroform; slightly soluble in ethyl acetate; practically insoluble in water.

Ichthammol: Reddish-brown to brownish-black, viscous fluid, having a strong, characteristic, empyreumatic odor. Miscible with water, with glycerin, and with fixed oils and fats. Partially soluble in alcohol and in ether.

Idarubicin Hydrochloride: Red-orange to red-brown powder. Soluble in methanol; slightly soluble in water; insoluble in acetone and in ethyl ether.

Iodoxuridine: White, crystalline, practically odorless powder. Slightly soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Ifosfamide: White, crystalline powder. Melts at about 40°. Very soluble in alcohol, in ethyl acetate, in isopropyl alcohol, in methanol, and in methylene chloride; freely soluble in water; very slightly soluble in hexanes.

Imidurea: White, odorless, tasteless powder. Soluble in water and in glycerin; sparingly soluble in propylene glycol; insoluble in most organic solvents.

Imipenem: White to tan-colored crystalline powder. Slightly soluble in water and in methanol.

Imipramine Hydrochloride: White to off-white, odorless or practically odorless, crystalline powder. Freely soluble in water and in alcohol; soluble in acetone; insoluble in ether and in benzene.

Inamrinone: Pale yellow to tan powder. It is odorless or has a faint odor. Slightly soluble in methanol; practically insoluble or insoluble in chloroform and in water.

Indapamide: White to off-white, crystalline powder. Melts between 167° and 170°. Soluble in methanol, in alcohol, in acetonitrile, in glacial acetic acid, and in ethyl acetate; very slightly soluble in ether and in chloroform; practically insoluble in water.

Indigotindisulfonate Sodium: Dusky, purplish-blue powder, or blue granules having a coppery luster. Is affected by light. Its solutions have a blue or bluish purple color. Slightly soluble in water and in alcohol; practically insoluble in most other organic solvents.

Indinavir Sulfate: White or almost white, hygroscopic powder. Freely soluble in water; soluble in methanol; practically insoluble in heptane.

Indocyanine Green: Olive-brown, dark green, blue-green, dark blue, or black powder. Is odorless or has a slight odor. Its solutions are deep emerald-green in color. The pH of a solution (1 in 200) is about 6. Its aqueous solutions are stable for about 8 hours. Soluble in water and in methanol; practically insoluble in most other organic solvents.

Indomethacin: Pale yellow to yellow-tan, crystalline powder, having not more than a slight odor. Is sensitive to light. Melts at about 162°. Exhibits polymorphism. Sparingly soluble in alcohol, in chloroform, and in ether; practically insoluble in water.

Influenza Virus Vaccine: Slightly turbid liquid or suspension, which may have a slight yellow or reddish tinge and may have an odor because of the preservative.

Inositol: White or almost white, crystalline powder. Very soluble in water; practically insoluble in alcohol absolute and in ether.

Insulin: White or practically white crystals. Soluble in solutions of dilute acids and alkalis.

Insulin Injection: The Injection containing, in each mL, not more than 100 USP Units is a clear, colorless or almost colorless liquid; the Injection containing, in each mL, 500 Units may be straw-colored. Contains between 0.1% and 0.25% (w/v) of either phenol or cresol. Contains between 1.4% and 1.8% (w/v) of glycerin.

Insulin Lispro: White or practically white crystals. Soluble in solutions of dilute acids and alkalis.

Isophane Insulin Suspension: White suspension of rod-shaped crystals, free from large aggregates of crystals fol-

lowing moderate agitation. Contains either (1) between 1.4% and 1.8% (w/v) of glycerin, between 0.15% and 0.17% (w/v) of metacresol, and between 0.06% and 0.07% (w/v) of phenol; or (2) between 1.4% and 1.8% (w/v) of glycerin and between 0.20% and 0.25% (w/v) of phenol. Contains between 0.15% and 0.25% (w/v) of dibasic sodium phosphate. When examined microscopically, the insoluble matter in the Suspension is crystalline, and contains not more than traces of amorphous material.

Insulin Zinc Suspension: Practically colorless suspension of a mixture of characteristic crystals predominantly between 10 and 40 μ m in maximum dimension and many particles that have no uniform shape and do not exceed 2 μ m in maximum dimension. Contains between 0.15% and 0.17% (w/v) of sodium acetate, between 0.65% and 0.75% (w/v) of sodium chloride, and between 0.09% and 0.11% (w/v) of methylparaben.

Extended Insulin Zinc Suspension: Practically colorless suspension of a mixture of characteristic crystals the maximum dimension of which is predominantly between 10 and 40 μ m. Contains between 0.15% and 0.17% (w/v) of sodium acetate, between 0.65% and 0.75% (w/v) of sodium chloride, and between 0.09% and 0.11% (w/v) of methylparaben.

Prompt Insulin Zinc Suspension: Practically colorless suspension of particles that have no uniform shape and the maximum dimension of which does not exceed 2 μ m. Contains between 0.15% and 0.17% (w/v) of sodium acetate, between 0.65% and 0.75% (w/v) of sodium chloride, and between 0.09% and 0.11% (w/v) of methylparaben.

Inulin: White, friable, chalk-like, amorphous, odorless, tasteless powder. Soluble in hot water; slightly soluble in cold water and in organic solvents.

Iodine: Heavy, grayish-black plates or granules, having a metallic luster and a characteristic odor. Freely soluble in carbon disulfide, in chloroform, in carbon tetrachloride, and in ether; soluble in alcohol and in solutions of iodides; sparingly soluble in glycerin; very slightly soluble in water.

Iodine Topical Solution: Transparent, reddish-brown liquid, having the odor of iodine.

Strong Iodine Solution: Transparent liquid having a deep brown color and having the odor of iodine.

Iodine Tincture: Transparent liquid having a reddish-brown color and the odor of iodine and of alcohol.

Sodium Iodide I 123 Capsules: Capsules may contain a small amount of solid or solids, or may appear empty.

Sodium Iodide I 123 Solution: Clear, colorless solution. Upon standing, both the Solution and the glass container may darken as a result of the effects of the radiation.

Iodinated I 125 Albumin Injection: Clear, colorless to slightly yellow solution. Upon standing, both the Albumin and the glass container may darken as a result of the effects of the radiation.

Iodinated I 131 Albumin Injection: Clear, colorless to slightly yellow solution. Upon standing, both the Albumin and the glass container may darken as a result of the effects of the radiation.

Iodinated I 131 Albumin Aggregated Injection: Dilute suspension of white to faintly yellow particles, which may settle on standing. The glass container may darken on standing, as a result of the effects of the radiation.

Sodium Rose Bengal I 131 Injection: Clear, deep-red solution.

Iodohippurate Sodium I 131 Injection: Clear, colorless solution. Upon standing, both the Injection and the glass container may darken as a result of the effects of the radiation.

Sodium Iodide I 131 Capsules: May contain a small amount of solid or solids, or may appear empty.

Sodium Iodide I 131 Solution: Clear, colorless solution. Upon standing, both the Solution and the glass container may darken as a result of the effects of the radiation.

Iodipamide: White, practically odorless, crystalline powder. Slightly soluble in alcohol; very slightly soluble in water, in chloroform, and in ether.

Iodipamide Meglumine Injection: Clear, colorless to pale yellow, slightly viscous liquid.

Iodixanol: White to off-white, amorphous, odorless, hygroscopic powder. Freely soluble in water.

Iodoform: Lustrous greenish yellow powder, or lustrous crystals. It is slightly volatile even at ordinary temperatures, and distills slowly with steam. Freely soluble in ether and in chloroform; soluble in boiling alcohol; sparingly soluble in alcohol, in glycerin, and in olive oil; practically insoluble in water. Melts to a brown liquid at about 115°, and decomposes at a higher temperature, emitting vapors of iodine.

Iodoquinol: Light yellowish to tan, microcrystalline powder not readily wetted by water. Is odorless or has a faint odor; is stable in air. Melts with decomposition. Sparingly soluble in alcohol and in ether; practically insoluble in water.

Iohexol: White to off-white, hygroscopic, odorless powder. Very soluble in water and in methanol; practically insoluble or insoluble in ether and in chloroform.

Iohexol Injection: Clear, colorless to pale yellow liquid.

Iopamidol: Practically odorless, white to off-white powder. Very soluble in water; sparingly soluble in methanol; practically insoluble in alcohol and in chloroform.

Iopanoic Acid: Cream-colored powder. Is tasteless or practically so, and has a faint, characteristic odor. Is affected by light. Soluble in alcohol, in chloroform, and in ether, and in solutions of alkali hydroxides and carbonates; insoluble in water.

Iophendylate: Colorless to pale yellow, viscous liquid, the color darkening on long exposure to air. Is odorless or has a faintly ethereal odor. Freely soluble in alcohol, in benzene, in chloroform, and in ether; very slightly soluble in water.

Iophendylate Injection: Colorless to pale yellow, viscous liquid, the color darkening on long exposure to air. Is odorless or has a faintly ethereal odor. Freely soluble in alcohol, in benzene, in chloroform, and in ether; very slightly soluble in water.

Iopromide: White to slightly yellow powder. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in alcohol, in acetone, and in ether.

Iothalamate Meglumine Injection: Clear, colorless to pale yellow, slightly viscous liquid.

Iothalamate Meglumine and Iothalamate Sodium Injection: Clear, colorless to pale yellow, slightly viscous liquid.

Iothalamate Sodium Injection: Clear, colorless to pale yellow, slightly viscous liquid.

Iothalamic Acid: White, odorless powder. Soluble in solutions of alkali hydroxides; slightly soluble in water and in alcohol.

Ioxilan: White to off-white, practically odorless powder. Soluble in water and in methanol.

Ioxilan Injection: Clear, colorless to pale yellow liquid.

Powdered Ipecac: Pale brown, weak yellow, or light olive-gray powder.

Ipodate Sodium: White to off-white, odorless, fine, crystalline powder. Freely soluble in water, in alcohol, and in methanol; very slightly soluble in chloroform.

Ipratropium Bromide: White to off-white, crystalline powder. Freely soluble in methanol; soluble in water; slightly soluble in alcohol.

Irbesartan: White to off-white, crystalline powder. Slightly soluble in alcohol and in methylene chloride; practically insoluble in water.

Irinotecan Hydrochloride: Pale yellow to yellow crystalline powder. Sparingly soluble in water and in alcohol; slightly soluble in most organic solvents.

Iron Dextran Injection: Dark brown, slightly viscous liquid.

Iron Sorbitex Injection: Clear liquid, having a dark brown color.

Isobutane: Colorless, flammable gas (boiling temperature is about –11°). Vapor pressure at 21° is about 2950 mm of mercury (31 psig). *NF category:* Aerosol propellant.

Isoetharine Inhalation Solution: Colorless or slightly yellow, slightly acid liquid, gradually turning dark on exposure to air and light.

Isoetharine Hydrochloride: White to off-white, odorless, crystalline solid. Melts between 196° and 208°, with decomposition. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether.

Isoetharine Mesylate: White or practically white, odorless crystals having a salty, bitter taste. Freely soluble in water; soluble in alcohol; practically insoluble in acetone and in ether.

Isoflurane: Clear, colorless, volatile liquid, having a slight odor. Boils at about 49°. Insoluble in water. Miscible with common organic solvents and with fats and oils.

Isofluorophate: Clear, colorless or faintly yellow liquid. Its vapor is extremely irritating to the eye and mucous membranes. Is decomposed by moisture, with the formation of hydrogen fluoride. Specific gravity is about 1.05. Soluble in alcohol and in vegetable oils; sparingly soluble in water.

Isoleucine: White, practically odorless crystals, having a slightly bitter taste. Soluble in water; slightly soluble in hot alcohol; insoluble in ether.

Isometheptene Mucate: White, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether.

Isoniazid: Colorless or white crystals or white, crystalline powder. Is odorless and is slowly affected by exposure to air and light. Freely soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether.

Isoniazid Injection: Clear, colorless to faintly greenish-yellow liquid. Gradually darkens on exposure to air and light. Tends to crystallize at low temperatures.

Isopropamide Iodide: White to pale yellow, crystalline powder, having a bitter taste. Freely soluble in chloroform and in alcohol; sparingly soluble in water; very slightly soluble in benzene and in ether.

Isopropyl Alcohol: Transparent, colorless, mobile, volatile liquid, having a characteristic odor and a slightly bitter taste. Is flammable. Miscible with water, with alcohol, with ether, and with chloroform. *NF category:* Solvent.

Azeotropic Isopropyl Alcohol: Transparent, colorless, mobile, volatile liquid, having a characteristic odor and a slightly bitter taste. Is flammable. Miscible with water, with alcohol, with ether, and with chloroform.

Isopropyl Myristate: Clear, practically colorless, oily liquid. Is practically odorless, and congeals at about 5°. Freely soluble in 90% alcohol; insoluble in water, in glycerin, and in propylene glycol. Miscible with most organic solvents and with fixed oils. *NF category:* Vehicle (oleaginous).

Isopropyl Palmitate: Colorless, mobile liquid having a very slight odor. Soluble in acetone, in castor oil, in chloroform, in cottonseed oil, in ethyl acetate, in alcohol, and in mineral oil; insoluble in water, in glycerin, and in propylene glycol. *NF category:* Vehicle (oleaginous).

Isoproterenol Inhalation Solution: Colorless or practically colorless, slightly acid liquid, gradually turning dark on exposure to air and light.

Isoproterenol Hydrochloride: White to practically white, odorless, crystalline powder, having a slightly bitter taste. Gradually darkens on exposure to air and light. Its solutions become pink to brownish pink on standing exposed to air, doing so almost immediately when rendered alkaline. Its solution (1 in 100) has a pH of about 5. Freely soluble in water; sparingly soluble in alcohol and less soluble in dehydrated alcohol; insoluble in chloroform and in ether.

Isoproterenol Hydrochloride Injection: Colorless or practically colorless liquid, gradually turning dark on exposure to air and light.

Isoproterenol Sulfate: White to practically white, odorless, crystalline powder. It gradually darkens on exposure to air and light. Its solutions become pink to brownish pink on standing exposed to air, doing so almost immediately when rendered alkaline. A solution (1 in 100) has a pH of about 5. Freely soluble in water; very slightly soluble in alcohol, in benzene, and in ether.

Isosorbide Concentrate: Colorless to slightly yellow liquid. Soluble in water and in alcohol.

Diluted Isosorbide Dinitrate: Ivory-white, odorless powder. [NOTE—Undiluted isosorbide dinitrate occurs as white, crystalline rosettes.] Undiluted isosorbide dinitrate is very soluble in acetone; freely soluble in chloroform; sparingly soluble in alcohol; very slightly soluble in water.

Isotretinoin: Yellow crystals. Soluble in chloroform; sparingly soluble in alcohol, in isopropyl alcohol, and in polyethylene glycol 400; practically insoluble in water.

Isosuprine Hydrochloride: White, odorless, crystalline powder, having a bitter taste. Melts at about 200°, with decomposition. Sparingly soluble in alcohol; slightly soluble in water.

Isradipine: Yellow, fine crystalline powder.

Itraconazole: A white or almost white powder. Freely soluble in methylene chloride; sparingly soluble in tetrahydrofuran; very slightly soluble in alcohol; practically insoluble in water.

Ivermectin: White to yellowish-white, crystalline powder. Slightly hygroscopic. Freely soluble in methanol and in methylene chloride; soluble in acetone and in acetonitrile; practically insoluble in hexane and in water.

Juniper Tar: Dark brown, clear, thick liquid, having a tarry odor and a faintly aromatic, bitter taste. Sparingly soluble in solvent hexane; very slightly soluble in water. One volume dissolves in 9 volumes of alcohol. Dissolves in 3 volumes of ether, leaving only a slight, flocculent residue. Miscible with amyl alcohol, with chloroform, and with glacial acetic acid.

Kanamycin Sulfate: White, odorless, crystalline powder. Freely soluble in water; insoluble in acetone, in ethyl acetate, and in benzene.

Kaolin: Soft, white or yellowish-white powder or lumps. Has an earthy or clay-like taste and, when moistened with water, assumes a darker color and develops a marked clay-like odor. Insoluble in water, in cold dilute acids, and in solutions of alkali hydroxides. *NF category:* Tablet and/or capsule diluent.

Ketamine Hydrochloride: White, crystalline powder, having a slight, characteristic odor. Freely soluble in water and in methanol; soluble in alcohol; sparingly soluble in chloroform.

Ketorolac Tromethamine: White to off-white, crystalline powder. Melts between 165° and 170°, with decomposition. Freely soluble in water and in methanol; slightly soluble in alcohol, in dehydrated alcohol, and in tetrahydrofuran; practically insoluble in acetone, in dichloromethane, in toluene, in ethyl acetate, in dioxane, in hexane, in butyl alcohol, and in acetonitrile.

Labetalol Hydrochloride: White to off-white powder. Melts at about 180°, with decomposition. Soluble in water and in alcohol; insoluble in ether and in chloroform.

Alpha-Lactalbumin: Free-flowing, slightly hygroscopic light cream-colored powder. Freely soluble in water; soluble in wide pH ranges; insoluble in methanol, in alcohol, in ether, and in acetone. *NF category:* Buffering agent; bulking agent for freeze-drying; coating agent; complexing agent; emulsifying and/or solubilizing agent; stiffening agent; suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; vehicle.

Lactic Acid: Colorless or yellowish, practically odorless, syrupy liquid. Is hygroscopic. When it is concentrated by boiling, lactic acid lactate is formed. Specific gravity is about 1.20. Insoluble in chloroform. Miscible with water, with alcohol, and with ether. *NF category:* Buffering agent.

Lactitol: A white or light brown, odorless crystal. Has a mild, sweet taste, and no aftertaste. *NF category:* Flavors and perfumes; tablet and/or capsule diluent.

Lactobionic Acid: White or almost white, crystalline powder with a melting point of about 125° with decomposition. Freely soluble in water; slightly soluble in glacial acetic acid, in anhydrous ethanol, and in methanol. *NF category:* Antioxidant.

Anhydrous Lactose: White or almost white powder. Freely soluble in water; practically insoluble in alcohol. *NF category:* Tablet and/or capsule diluent.

Lactose Monohydrate: White, free-flowing powder. Freely but slowly soluble in water; practically insoluble in alcohol. *NF category:* Tablet and/or capsule diluent.

Lactulose Concentrate: Colorless to amber syrupy liquid, which may exhibit some precipitation and darkening upon standing. Miscible with water.

Lamivudine: White to off-white solid. Soluble in water. Melts at about 176°.

Lamotrigine: A white to pale cream-colored powder. Slightly soluble in 0.1 N hydrochloric acid, in acetone, in methanol, and in water.

Lanolin: Yellow, tenacious, unctuous mass, having a slight, characteristic odor. Freely soluble in ether and in chloroform; soluble in hot alcohol; sparingly soluble in cold alcohol; insoluble in water, but mixes without separation with about twice its weight of water. *NF category:* Ointment base.

Lanolin Alcohols: Hard, waxy, amber solid, having a characteristic odor. Freely soluble in chloroform, in ether, and in petroleum ether; slightly soluble in alcohol; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Lansoprazole: White to brownish-white powder. Freely soluble in dimethylformamide; practically insoluble in water. Melts at about 166°, with decomposition.

Add the following:

■ **Latanoprost:** Colorless to slightly yellow oil. Very soluble in acetonitrile; freely soluble in acetone, in ethanol, in ethyl acetate, in isopropanol, in methanol, and in octanol; practically insoluble in water. ■ *USP36*

Lauroyl Polyoxylglycerides: Pale yellow, waxy liquids. Freely soluble in methylene chloride. Dispersible in hot water. *NF category:* Ointment base; solvent.

Lecithin: The consistency of both natural grades and refined grades of lecithin may vary from plastic to fluid, depending upon free fatty acid and oil content, and upon the presence or absence of other diluents. Its color varies from light yellow to brown, depending on the source, on crop variations, and on whether it is bleached or unbleached. It is odorless or has a characteristic, slight nut-like odor and a bland taste. Practically insoluble in water, but it readily hydrates to form emulsions. The oil-free phosphatides are soluble in fatty acids, but are practically insoluble in fixed

oils. When all phosphatide fractions are present, lecithin is sparingly soluble in alcohol and practically insoluble in acetone. *NF category:* Emulsifying and/or solubilizing agent.

Leflunomide: White to almost white powder. Freely soluble in methanol, in alcohol, in 2-propanol, in ethyl acetate, in acetone, and in acetonitrile; practically insoluble in water.

Letrozole: White to yellowish, crystalline powder. Freely soluble in dichloromethane; slightly soluble in alcohol; practically insoluble in water.

Leucine: White, practically odorless, tasteless crystals. Sparingly soluble in water; insoluble in ether.

Leucovorin Calcium: Yellowish-white or yellow, odorless powder. Very soluble in water; practically insoluble in alcohol.

Leucovorin Calcium Injection: Clear, yellowish solution.

Levamisole Hydrochloride: White or almost white, crystalline powder. Freely soluble in water; soluble in alcohol; slightly soluble in methylene chloride; practically insoluble in ether.

Levetiracetam: White to almost white powder. Very soluble in water; soluble in acetonitrile; practically insoluble in hexane.

Levmetamfetamine: Clear, practically colorless liquid.

Levobunolol Hydrochloride: White crystalline, odorless powder. Soluble in water and in methanol; slightly soluble in alcohol and in chloroform.

Levocarnitine: White crystals or crystalline powder. Hygroscopic. Freely soluble in water, and in hot alcohol; practically insoluble in acetone, in ether, and in benzene.

Levodopa: White to off-white, odorless, crystalline powder. In the presence of moisture, is rapidly oxidized by atmospheric oxygen and darkens. Freely soluble in 3 N hydrochloric acid; slightly soluble in water; insoluble in alcohol.

Levofloxacin: Light yellowish-white to yellow-white crystals or crystalline powder. Soluble in dimethylsulfoxide and in acetic acid; sparingly soluble in water, in acetone, and in methanol; practically insoluble in glycerin and in *n*-octanol.

Levonordefrin: White to buff-colored, odorless, crystalline solid. Melts at about 210°. Freely soluble in aqueous solutions of mineral acids; slightly soluble in acetone, in chloroform, in alcohol, and in ether; practically insoluble in water.

Levonorgestrel: White or practically white, odorless powder. Soluble in chloroform; slightly soluble in alcohol; practically insoluble in water.

Levorphanol Tartrate: Practically white, odorless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. Melts, in a sealed tube, at about 110°, with decomposition.

Levothyroxine Sodium: Light yellow to buff-colored, odorless, tasteless, hygroscopic powder. Is stable in dry air but may assume a slight pink color upon exposure to light. The pH of a saturated solution is about 8.9. Soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates; slightly soluble in alcohol; very slightly soluble in water; insoluble in acetone, in chloroform, and in ether.

Lidocaine: White or slightly yellow, crystalline powder. Has a characteristic odor and is stable in air. Very soluble in alcohol and in chloroform; freely soluble in benzene and in ether; practically insoluble in water. Dissolves in oils.

Lidocaine Hydrochloride: White, odorless, crystalline powder, having a slightly bitter taste. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Lime: Hard, white or grayish-white masses or granules, or white or grayish white powder. Is odorless. Slightly soluble in water; very slightly soluble in boiling water.

Lincomycin Hydrochloride: White or practically white, crystalline powder. Is odorless or has a faint odor. Is stable

in the presence of air and light. Its solutions are acid and dextrorotatory. Freely soluble in water; soluble in dimethylformamide; very slightly soluble in acetone.

Lincomycin Hydrochloride Injection: Clear, colorless to slightly yellow solution, having a slight odor.

Lincomycin Hydrochloride Soluble Powder: White to off-white, or light tan free-flowing, fine powder.

Lindane: White, crystalline powder, having a slight, musty odor. Freely soluble in chloroform; soluble in dehydrated alcohol; sparingly soluble in ether; slightly soluble in ethylene glycol; practically insoluble in water.

Linoleoyl Polyoxylglycerides: Amber, oily liquids. May develop deposit after prolonged storage periods at 20°. Freely soluble in methylene chloride; practically insoluble but dispersible in water. *NF category:* Ointment base; solvent.

Liothyronine Sodium: Light tan, odorless, crystalline powder. Slightly soluble in alcohol; very slightly soluble in water; practically insoluble in most other organic solvents.

Lisinopril: White, crystalline powder. Melts at about 160°, with decomposition. Soluble in water; sparingly soluble in methanol; practically insoluble in alcohol, in acetone, in acetonitrile, and in chloroform.

Lithium Carbonate: White, granular, odorless powder. Sparingly soluble in water; very slightly soluble in alcohol. Dissolves, with effervescence, in dilute mineral acids.

Lithium Citrate: White, odorless, deliquescent powder or granules, having a cooling, faintly alkaline taste. Freely soluble in water; slightly soluble in alcohol.

Loperamide Hydrochloride: White to slightly yellow powder. Melts at about 225°, with some decomposition. Freely soluble in methanol and in chloroform; slightly soluble in water and in dilute acids; very slightly soluble in isopropyl alcohol.

Lopinavir: White powder. Freely soluble in methanol and alcohol; soluble in isopropanol; practically insoluble in water.

Loratadine: White to off-white powder. Freely soluble in acetone, in chloroform, in methanol, and in toluene; insoluble in water.

Lorazepam: White or practically white, practically odorless powder. Sparingly soluble in alcohol; slightly soluble in chloroform; insoluble in water.

Losartan Potassium: White to off-white powder. Freely soluble in water; sparingly soluble in isopropyl alcohol; slightly soluble in acetonitrile.

Lovastatin: White to off-white, crystalline powder. Freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methanol; sparingly soluble in alcohol; practically insoluble in hexane; insoluble in water.

Loxapine Succinate: White to yellowish, crystalline powder. Is odorless.

Lutein: Red, crystalline powder. Soluble in ethanol, in ethyl acetate, and in methylene chloride; partially soluble in hexane.

Lysine Acetate: White, odorless crystals or crystalline powder, having an acid taste. Freely soluble in water.

Lysine Hydrochloride: White, odorless powder. Freely soluble in water.

Mafenide Acetate: White to pale yellow, crystalline powder. Freely soluble in water.

Magaldrate: White, odorless, crystalline powder. Soluble in dilute solutions of mineral acids; insoluble in water and in alcohol.

Milk of Magnesia: White, opaque, more or less viscous suspension from which varying proportions of water usually separate on standing. pH is about 10.

Magnesium Aluminometasilicate: White powder or granules having an amorphous structure. Very slightly solu-

ble in acids and in alkalies; practically insoluble in water and in alcohol.

Magnesium Aluminosilicate: White powder or granules having an amorphous structure. Very slightly soluble in acids and in alkalies; practically insoluble in water and in alcohol.

Magnesium Aluminum Silicate: Odorless, tasteless, fine (micronized) powder, small cream to tan granules, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerin. *NF category:* Suspending and/or viscosity-increasing agent.

Magnesium Carbonate: Light, white, friable masses or bulky, white powder. Is odorless, and is stable in air. Practically insoluble in water to which, however, it imparts a slightly alkaline reaction; insoluble in alcohol, but is dissolved by dilute acids with effervescence.

Magnesium Chloride: Colorless, odorless, deliquescent flakes or crystals, which lose water when heated to 100° and lose hydrochloric acid when heated to 110°. Very soluble in water; freely soluble in alcohol.

Magnesium Citrate Oral Solution: Colorless to slightly yellow, clear, effervescent liquid, having a sweet, acidulous taste and a lemon flavor.

Magnesium Gluconate: Colorless crystals or white powder or granules. Is odorless and tasteless. Freely soluble in water; very slightly soluble in alcohol; insoluble in ether.

Magnesium Hydroxide: Bulky, white powder. Soluble in dilute acids; practically insoluble in water and in alcohol.

Magnesium Oxide: Very bulky, white powder or relatively dense, white powder or granulated powder. Soluble in dilute acids; practically insoluble in water; insoluble in alcohol.

Magnesium Phosphate: White, odorless, tasteless powder. Soluble in diluted mineral acids; practically insoluble in water.

Magnesium Salicylate: White, odorless, efflorescent, crystalline powder. Freely soluble in methanol; soluble in alcohol and in water; slightly soluble in ether.

Magnesium Silicate: Fine, white, odorless, tasteless powder, free from grittiness. Insoluble in water and in alcohol. Is readily decomposed by mineral acids. *NF category:* Glidant and/or anticaking agent.

Magnesium Stearate: Very fine, light, white powder, slippery to touch. Insoluble in water, in alcohol, and in ether. *NF category:* Tablet and/or capsule lubricant.

Magnesium Sulfate: Small, colorless crystals, usually needle-like, with a cooling, saline, bitter taste. It effloresces in warm, dry air. Very soluble in boiling water; freely soluble in water; freely (and slowly) soluble in glycerin; sparingly soluble in alcohol.

Magnesium Trisilicate: Fine, white, odorless, tasteless powder, free from grittiness. Insoluble in water and in alcohol. Is readily decomposed by mineral acids.

Malathion: Clear, colorless, or slightly yellowish liquid, having a characteristic odor. Congeals at about 2.9°. Slightly soluble in water. Miscible with alcohols, with esters, with ketones, with ethers, with aromatic and alkylated aromatic hydrocarbons, and with vegetable oils.

Maleic Acid: White, crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in ether.

Malic Acid: White or practically white, crystalline powder or granules, having a strongly acid taste. Melts at about 130°. Very soluble in water; freely soluble in alcohol. *NF category:* Acidifying agent.

Maltitol: White, crystalline powder. Very soluble in water; practically insoluble in ethanol. *NF category:* Humectant; sweetening agent; tablet and/or capsule diluent.

Maltodextrin: White, hygroscopic powder or granules. Freely soluble or readily dispersible in water; slightly soluble

to insoluble in anhydrous alcohol. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent.

Maltol: A white, crystalline powder having a characteristic caramel-butterscotch odor, suggestive of a fruity-strawberry aroma in dilute solution. One g dissolves in about 82 mL of water, in 21 mL of alcohol, in 80 mL of glycerin, and in 28 mL of propylene glycol. *NF category:* Flavors and perfumes.

Maltose: Maltose occurs in either the anhydrous state or as a monohydrate. It is a white, crystalline powder, odorless, and has a sweet taste. Very slightly soluble in ethanol; freely soluble in water; slightly soluble in methanol; practically insoluble in ether.

Mangafodipir Trisodium: Pale yellow crystals or crystalline powder. Freely soluble in water; sparingly soluble in methanol; slightly soluble in chloroform; very slightly soluble in alcohol and in acetone.

Manganese Chloride: Large, irregular, pink, odorless, translucent crystals. Soluble in water and in alcohol; insoluble in ether.

Manganese Chloride for Oral Solution: Off-white to tan-colored powder with a strawberry odor. Soluble in water.

Manganese Sulfate: Pale red, slightly efflorescent crystals, or purple, odorless powder. Soluble in water; insoluble in alcohol.

Mannitol: White, crystalline powder or free-flowing granules. Is odorless and has a sweet taste. Freely soluble in water; soluble in alkaline solutions; slightly soluble in pyridine; very slightly soluble in alcohol; practically insoluble in ether. *NF category:* Sweetening agent; tablet and/or capsule diluent; tonicity agent; bulking agent for freeze-drying.

Maprotiline Hydrochloride: Fine, white to off-white, crystalline powder. Is practically odorless. Freely soluble in methanol and in chloroform; slightly soluble in water; practically insoluble in isooctane.

Mazindol: White to off-white, crystalline powder, having not more than a faint odor. Slightly soluble in methanol and in chloroform; insoluble in water.

Delete the following:

■**Measles Virus Vaccine Live:** Solid having the characteristic appearance of substances dried from the frozen state. Undergoes loss of potency on exposure to sunlight. The Vaccine is to be constituted with a suitable diluent just prior to use. ■1S (USP36)

Delete the following:

■**Measles, Mumps, and Rubella Virus Vaccine Live:** Solid having the characteristic appearance of substances dried from the frozen state. The Vaccine is to be constituted with a suitable diluent just prior to use. Constituted vaccine undergoes loss of potency on exposure to sunlight. ■1S (USP36)

Delete the following:

■**Measles and Rubella Virus Vaccine Live:** Solid having the characteristic appearance of substances dried from the frozen state. The Vaccine is to be constituted with a suitable diluent just prior to use. Constituted vaccine undergoes loss of potency on exposure to sunlight. ■1S (USP36)

Mebendazole: White to slightly yellow powder. Is almost odorless. Melts at about 290°. Freely soluble in formic acid; practically insoluble in water, in dilute solutions of mineral acids, in alcohol, in ether, and in chloroform.

Mechlorethamine Hydrochloride: White, crystalline powder. Is hygroscopic.

Meclizine Hydrochloride: White or slightly yellowish, crystalline powder. Has a slight odor and is tasteless. Slightly soluble in dilute acids and in alcohol; practically insoluble in water and in ether; freely soluble in chloroform, in pyridine, and in acid-alcohol-water mixtures.

Meclofenamate Sodium: A white to creamy white, odorless to almost odorless, crystalline powder. Freely soluble in water, the solution sometimes being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; soluble in methanol; slightly soluble in chloroform; practically insoluble in ether. The solution is clear above pH 11.5.

Medroxyprogesterone Acetate: White to off-white, odorless, crystalline powder. Melts at about 205°. Is stable in air. Freely soluble in chloroform; soluble in acetone and in dioxane; sparingly soluble in alcohol and in methanol; slightly soluble in ether; insoluble in water.

Mefenamic Acid: White to off-white, crystalline powder. Melts at about 230°, with decomposition. Soluble in solutions of alkali hydroxides; sparingly soluble in chloroform; slightly soluble in alcohol and in methanol; practically insoluble in water.

Mefloquine Hydrochloride: White or slightly yellow, crystalline powder. It exhibits polymorphism. Freely soluble in methanol; soluble in alcohol; very slightly soluble in water.

Megestrol Acetate: White to creamy white, tasteless and essentially odorless, crystalline powder. Very soluble in chloroform; soluble in acetone; sparingly soluble in alcohol; slightly soluble in ether and in fixed oils; insoluble in water. Is unstable under aqueous conditions at pH 7 or above.

Meglumine: White to faintly yellowish-white, odorless crystals or powder. Freely soluble in water; sparingly soluble in alcohol.

Melengestrol Acetate: White to light yellow, crystalline powder. Freely soluble in chloroform and in ethyl acetate; slightly soluble in alcohol; insoluble in water.

Meloxicam: Pale yellow powder. Soluble in dimethylformamide; slightly soluble in acetone; very slightly soluble in methanol and in alcohol; practically insoluble in water.

Melphalan: Off-white to buff powder, having a faint odor. Melts at about 180°, with decomposition. Soluble in dilute mineral acids; slightly soluble in alcohol and in methanol; practically insoluble in water, in chloroform, and in ether.

Menadiol Sodium Diphosphate: White to pink powder, having a characteristic odor. Is hygroscopic. Its solutions are neutral or slightly alkaline to litmus, having a pH of about 8. Very soluble in water; insoluble in alcohol.

Menadione: Bright yellow, crystalline, practically odorless powder. Is affected by sunlight. Soluble in vegetable oils; sparingly soluble in chloroform and in alcohol; practically insoluble in water.

Menthol: Colorless, hexagonal crystals, usually needle-like, or in fused masses, or crystalline powder. Has a pleasant, peppermint-like odor. Very soluble in alcohol, in chloroform, in ether, and in solvent hexane; freely soluble in glacial acetic acid, in mineral oil, and in fixed and volatile oils; slightly soluble in water. *NF category:* Flavors and perfumes.

Meperidine Hydrochloride: Fine, white, crystalline, odorless powder. The pH of a solution (1 in 20) is about 5. Very soluble in water; soluble in alcohol; sparingly soluble in ether.

Mephobarbital: White, odorless, crystalline powder, having a bitter taste. Its saturated solution is acid to litmus. Soluble in chloroform and in solutions of fixed alkali hydroxides and carbonates; slightly soluble in water, in alcohol, and in ether.

Mepivacaine Hydrochloride: White, odorless, crystalline solid. The pH of a solution (1 in 50) is about 4.5. Freely soluble in water and in methanol; very slightly soluble in chloroform; practically insoluble in ether.

Meprobamate: White powder, having a characteristic odor and a bitter taste. Freely soluble in acetone and in alcohol; slightly soluble in water; practically insoluble or insoluble in ether.

Mercaptopurine: Yellow, odorless or practically odorless, crystalline powder. Melts at a temperature exceeding 308°, with decomposition. Soluble in hot alcohol and in dilute alkali solutions; slightly soluble in 2 N sulfuric acid; insoluble in water, in acetone, and in ether.

Ammoniated Mercury: White, pulverulent pieces or white, amorphous powder. Is odorless, and is stable in air, but darkens on exposure to light. Readily soluble in warm hydrochloric, nitric, and acetic acids; insoluble in water, and in alcohol.

Change to read:

Meropenem: Colorless to white or light yellow crystals or crystalline powder. USP36 Soluble in dimethylformamide and in 5% dibasic potassium phosphate solution; sparingly soluble in water and in 5% monobasic potassium phosphate solution; practically insoluble in alcohol, in acetone, in methylene chloride, and in ether. USP36

Mesalamine: Light tan to pink colored, needle-shaped crystals. Color may darken on exposure to air. Is odorless or may have a slight characteristic odor. Soluble in dilute hydrochloric acid and in dilute alkali hydroxides; slightly soluble in water; very slightly soluble in methanol, in dehydrated alcohol, and in acetone; practically insoluble in *n*-butyl alcohol, in chloroform, in ether, in ethyl acetate, in *n*-hexane, in methylene chloride, and in *n*-propyl alcohol.

Mesna: White or slightly yellow crystalline powder; hygroscopic. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane.

Mesoridazine Besylate: White to pale yellowish powder, having not more than a faint odor. Melts at about 178°, with decomposition. Freely soluble in water, in chloroform, and in methanol.

Mestranol: White to creamy white, odorless, crystalline powder. Freely soluble in chloroform; soluble in dioxane; sparingly soluble in dehydrated alcohol; slightly soluble in methanol; insoluble in water.

Metaproterenol Sulfate: White to off-white, crystalline powder. Freely soluble in water.

Metformin Hydrochloride: White, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in methylene chloride.

Methacholine Chloride: Colorless or white crystals, or white, crystalline powder. Is odorless or has a slight odor, and is very hygroscopic. Its solutions are neutral to litmus. Very soluble in water; freely soluble in alcohol and in chloroform.

Methacrylic Acid Copolymer: White powder having a faint, characteristic odor. The polymer is soluble in diluted alkali, in simulated intestinal fluid TS, and in buffer solutions of pH 7 and above. The solubility between pH 5.5 and pH 7 depends on the content of methacrylic acid units in the copolymer. The polymer is freely soluble to soluble in methanol, in alcohol, in isopropyl alcohol, and in acetone, each of which contains not less than 3% of water; insoluble in water, in diluted acids, in simulated gastric fluid TS, and in buffer solutions of up to pH 5. *NF category:* Coating agent.

Methacrylic Acid Copolymer Dispersion: Milky-white liquid of low viscosity. It is miscible with water in any proportion; the milky-white appearance is retained. A clear or slightly opalescent, viscous solution is obtained on mixing one part with five parts of acetone, alcohol, or isopropyl alcohol; the polymer substance is first precipitated, but then dissolves in the excess organic solvent. A clear or slightly opalescent, viscous solution is obtained on mixing one part with two parts of 1 N sodium hydroxide.

Methacrylic Acid and Ethyl Acrylate Copolymer:

White powder having a faint, characteristic odor. Soluble to freely soluble in methanol, in alcohol, in isopropyl alcohol, and in acetone, each of which contains not less than 3% of water; soluble in diluted alkali, in simulated intestinal fluid TS, and in buffer solutions of pH 7 and above; insoluble in water, in diluted acids, in simulated gastric fluid TS, and in buffer solutions of up to pH 5. The solubility between pH 5.5 and pH 7 depends on the content of methacrylic acid units in the copolymer. *NF category:* Coating agent; film-forming agent.

Partially-Neutralized Methacrylic Acid and Ethyl

Acrylate Copolymer: White or almost white, free-flowing powder. Freely soluble in alcohol, in methanol, and in a 40 g/L solution of sodium hydroxide; soluble in solutions at pH values above pH 5.5 under salt formation; practically insoluble in ethyl acetate and in acidic aqueous solutions. *NF category:* Coating agent; film-forming agent.

Methacrylic Acid and Methyl Methacrylate Copolymer:

White powder having a faint, characteristic odor. Soluble to freely soluble in methanol, in alcohol, in isopropyl alcohol, and in acetone, each of which contains not less than 3% of water; soluble in diluted alkali, in simulated intestinal fluid TS, and in buffer solutions of pH 7 and above; insoluble in water, in diluted acids, in simulated gastric fluid TS, and in buffer solutions of up to pH 5. The solubility between pH 5.5 and pH 7 depends on the content of methacrylic acid units in the copolymer. *NF category:* Coating agent; film-forming agent.

Methacycline Hydrochloride: Yellow to dark yellow, crystalline powder. Soluble in water.

Methadone Hydrochloride: Colorless crystals or white, crystalline, odorless powder. Freely soluble in alcohol and in chloroform; soluble in water; practically insoluble in ether and in glycerin.

Methadone Hydrochloride Oral Concentrate: Clear to slightly hazy, syrupy liquid.

Methamphetamine Hydrochloride: White crystals or white, crystalline powder. Is odorless or practically so. Its solutions have a pH of about 6. Freely soluble in water, in alcohol, and in chloroform; very slightly soluble in absolute ether.

Methazolamide: White or faintly yellow, crystalline powder having a slight odor. Melts at about 213°. Soluble in dimethylformamide; slightly soluble in acetone; very slightly soluble in water and in alcohol.

Methdilazine Hydrochloride: Light tan, crystalline powder, having a slight, characteristic odor. Freely soluble in water, in alcohol, and in chloroform.

Methenamine: Colorless, lustrous crystals or white, crystalline powder. Is practically odorless. When brought into contact with fire, it readily ignites, burning with a smokeless flame. It sublimates at about 260°, without melting. Its solutions are alkaline to litmus. Freely soluble in water; soluble in alcohol and in chloroform.

Methenamine Mandelate: White, crystalline powder. Has a sour taste and is practically odorless. Its solutions have a pH of about 4. Melts at about 127°, with decomposition. Very soluble in water; soluble in alcohol and in chloroform; slightly soluble in ether.

Methimazole: White to pale buff, crystalline powder, having a faint, characteristic odor. Its solutions are practically neutral to litmus. Freely soluble in water, in alcohol, and in chloroform; slightly soluble in ether.

Methionine: White crystals, having a characteristic odor and taste. Soluble in water, in warm dilute alcohol, and in dilute mineral acids; insoluble in ether, in absolute alcohol, in benzene, and in acetone (L-form).

Methocarbamol: White powder, odorless, or having a slight characteristic odor. Melts at about 94°, or, if previously ground to a fine powder, melts at about 90°. Soluble

in alcohol only with heating; sparingly soluble in water and in chloroform; insoluble in benzene and in *n*-hexane.

Methohexital: White to faintly yellowish-white, crystalline, odorless powder. Slightly soluble in alcohol, in chloroform, and in dilute alkalies; very slightly soluble in water.

Methohexital Sodium for Injection: White to off-white, hygroscopic powder. Is essentially odorless.

Methotrexate: Orange-brown, or yellow, crystalline powder. Freely soluble in dilute solutions of alkali hydroxides and carbonates; slightly soluble in 6 N hydrochloric acid; practically insoluble in water, in alcohol, in chloroform, and in ether.

Methotrimeprazine: Fine, white, practically odorless, crystalline powder. Melts at about 126°. Freely soluble in chloroform, in ether, and in boiling alcohol; sparingly soluble in methanol and in alcohol at 25°; practically insoluble in water.

Methoxsalen: White to cream-colored, fluffy, needle-like crystals. Is odorless. Freely soluble in chloroform; soluble in boiling alcohol, in acetone, in acetic acid, in propylene glycol, and in benzene; sparingly soluble in boiling water and in ether; practically insoluble in water.

Methoxsalen Topical Solution: Clear, colorless liquid.

Methoxyflurane: Clear, practically colorless, mobile liquid, having a characteristic odor. Boils at about 105°. Miscible with alcohol, with acetone, with chloroform, with ether, and with fixed oils.

Methsuximide: White to grayish white, crystalline powder. Is odorless, or has not more than a slight odor. Very soluble in chloroform; freely soluble in alcohol and in ether; slightly soluble in hot water.

Methylclothiazide: White or practically white, crystalline powder. Is odorless, or has a slight odor. Freely soluble in acetone and in pyridine; sparingly soluble in methanol; slightly soluble in alcohol; very slightly soluble in water, in chloroform, and in benzene.

Methyl Alcohol: Clear, colorless liquid, having a characteristic odor. Is flammable. Miscible with water, with alcohol, with ether, with benzene, and with most other organic solvents. *NF category:* Solvent.

Methyl Benzylidene Camphor: A white, fine crystalline powder. Very soluble in chloroform; freely soluble in alcohol; practically insoluble in water.

Methyl Isobutyl Ketone: Transparent, colorless, mobile, volatile liquid, having a faint ketonic and camphoraceous odor. Slightly soluble in water. Miscible with alcohol, with ether, and with benzene. *NF category:* Alcohol denaturant; solvent.

Methyl Salicylate: Colorless, yellowish, or reddish liquid, having the characteristic odor and taste of wintergreen. It boils between 219° and 224°, with some decomposition. Soluble in alcohol and in glacial acetic acid; slightly soluble in water. *NF category:* Flavors and perfumes.

Methylbenzethonium Chloride: White, hygroscopic crystals, having a mild odor. Its solutions are neutral or slightly alkaline to litmus. Very soluble in water, in alcohol, and in ether; practically insoluble in chloroform.

Methylcellulose: White, fibrous powder or granules. Its aqueous suspensions are neutral to litmus. It swells in water and produces a clear to opalescent, viscous, colloidal suspension. Soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform; insoluble in alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Methyldopa: White to yellowish-white, odorless, fine powder, which may contain friable lumps. Very soluble in 3 N hydrochloric acid; sparingly soluble in water; slightly soluble in alcohol; practically insoluble in ether.

Methyldopate Hydrochloride: White or practically white, odorless or practically odorless, crystalline powder.

Freely soluble in water, in alcohol, and in methanol; slightly soluble in chloroform; practically insoluble in ether.

Methylene Blue: Dark green crystals or crystalline powder having a bronze-like luster. Is odorless or practically so, and is stable in air. Its solutions in water and in alcohol are deep blue in color. Soluble in water and in chloroform; sparingly soluble in alcohol.

Methylene Chloride: Clear, colorless, mobile liquid, having an odor resembling that of chloroform. Miscible with alcohol, with ether, and with fixed and volatile oils. *NF category:* Solvent.

Methylergonovine Maleate: White to pinkish-tan, microcrystalline powder. Is odorless. Slightly soluble in water and in alcohol; very slightly soluble in chloroform and in ether.

Methylparaben: White, crystalline powder or colorless crystals. Freely soluble in alcohol and in methanol; slightly soluble in water. *NF category:* Antimicrobial preservative.

Methylparaben Sodium: White, hygroscopic powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. *NF category:* Antimicrobial preservative.

Methylphenidate Hydrochloride: White, odorless, fine, crystalline powder. Its solutions are acid to litmus. Freely soluble in water and in methanol; soluble in alcohol; slightly soluble in chloroform and in acetone.

Methylprednisolone: White to practically white, odorless, crystalline powder. Melts at about 240°, with some decomposition (see *Melting Range or Temperature* <741>). Sparingly soluble in alcohol, in dioxane, and in methanol; slightly soluble in acetone and in chloroform; very slightly soluble in ether; practically insoluble in water.

Methylprednisolone Acetate: White or practically white, odorless, crystalline powder. Melts at about 225°, with some decomposition (see *Melting Range or Temperature* <741>). Soluble in dioxane; sparingly soluble in acetone, in alcohol, in chloroform, and in methanol; slightly soluble in ether; practically insoluble in water.

Methylprednisolone Hemisuccinate: White or nearly white, odorless or nearly odorless, hygroscopic solid. Freely soluble in alcohol; soluble in acetone; very slightly soluble in water.

Methylprednisolone Sodium Succinate: White or nearly white, odorless, hygroscopic, amorphous solid. Very soluble in water and in alcohol; very slightly soluble in acetone; insoluble in chloroform.

Methylpyrrolidone: A clear, colorless liquid. Miscible with water and with most organic solvents including alcohol, ketones, and aromatic and chlorinated hydrocarbons. Boiling point: about 202°. Refractive index: about 1.469. *NF category:* Solvent.

Methylsulfonylmethane: White powder or flake crystal. Melts at about 109°. Freely soluble in water, in methanol, in alcohol, and in acetone; sparingly soluble in ether.

Methyltestosterone: White or creamy white crystals or crystalline powder. Is odorless and is stable in air, but is slightly hygroscopic. Is affected by light. Soluble in alcohol, in methanol, in ether, and in other organic solvents; sparingly soluble in vegetable oils; practically insoluble in water.

Methysergide Maleate: White to yellowish-white or reddish-white, crystalline powder. Is odorless or has not more than a slight odor. Slightly soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether.

Metoclopramide Hydrochloride: White or practically white, crystalline, odorless or practically odorless powder. Very soluble in water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether.

Metoprolol Succinate: White to off-white powder. Freely soluble in water; soluble in methanol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol.

Metoprolol Tartrate: White, crystalline powder. Very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; insoluble in ether.

Metronidazole: White to pale yellow, odorless crystals or crystalline powder. Is stable in air, but darkens on exposure to light. Soluble in dilute hydrochloric acid (1 in 2); sparingly soluble in water and in alcohol; slightly soluble in ether and in chloroform.

Metronidazole Benzoate: White to slightly yellow, crystalline powder. Freely soluble in methylene chloride; soluble in acetone; slightly soluble in alcohol; very slightly soluble in ethyl ether; practically insoluble in water.

Metyrapone: White to light amber, fine, crystalline powder, having a characteristic odor. Darkens on exposure to light. Soluble in methanol and in chloroform; sparingly soluble in water. It forms water-soluble salts with acids.

Mexiletine Hydrochloride: White powder. Freely soluble in dehydrated alcohol and in water; slightly soluble in acetonitrile; practically insoluble in ether. Optically inactive (1 in 20 solution in water).

Mezlocillin Sodium: White to pale yellow, crystalline powder. Freely soluble in water.

Mibolerone: White to off-white powder. Slightly soluble in chloroform, in dioxane, and in methylene chloride; practically insoluble in water (0.0454 mg per mL at 37°).

Miconazole: White to pale cream powder. Melts in the range of 78° to 88°. May exhibit polymorphism. Freely soluble in alcohol, in methanol, in isopropyl alcohol, in acetone, in propylene glycol, in chloroform, and in dimethylformamide; soluble in ether; insoluble in water.

Miconazole Nitrate: White or practically white, crystalline powder, having not more than a slight odor. Melts in the range of 178° to 183°, with decomposition. Freely soluble in dimethyl sulfoxide; soluble in dimethylformamide; sparingly soluble in methanol; slightly soluble in alcohol, in chloroform, and in propylene glycol; very slightly soluble in water and in isopropyl alcohol; insoluble in ether.

Midazolam: White or yellowish powder. The hydrochloride salt of midazolam is soluble in aqueous solutions. Insoluble in water.

Midodrine Hydrochloride: White crystalline powder. Soluble in water; sparingly soluble in methanol.

Milrinone: White to tan, crystalline solid. Is hygroscopic. Freely soluble in dimethyl sulfoxide; very slightly soluble in methanol; practically insoluble in water and in chloroform.

Mineral Oil: Colorless, transparent, oily liquid, free or practically free from fluorescence. Is odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated. Soluble in volatile oils; insoluble in water and in alcohol. Miscible with most fixed oils but not with castor oil. *NF category:* Solvent; vehicle (oleaginous).

Light Mineral Oil: Colorless, transparent, oily liquid, free, or practically free, from fluorescence. Is odorless and tasteless when cold, and develops not more than a faint odor of petroleum when heated. Soluble in volatile oils; insoluble in water and in alcohol. Miscible with most fixed oils, but not with castor oil. *NF category:* Tablet and/or capsule lubricant; vehicle (oleaginous).

Minocycline Hydrochloride: Yellow, crystalline powder. Soluble in solutions of alkali hydroxides and carbonates; sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Minoxidil: White to off-white, crystalline powder. Melts in the approximate range of between 248° and 268°, with decomposition. Soluble in alcohol and in propylene glycol; sparingly soluble in methanol; slightly soluble in water; practically insoluble in chloroform, in acetone, in ethyl acetate, and in hexane.

Mirtazapine: White to creamy white, crystalline powder. Freely soluble in methanol and in toluene; soluble in ethyl ether; sparingly soluble in *n*-hexane; practically insoluble in water.

Misoprostol: Clear, colorless or light yellow viscous liquid. Very slightly soluble in water.

Mitomycin: Blue-violet, crystalline powder. Soluble in acetone, in methanol, in butyl acetate, and in cyclohexanone; slightly soluble in water.

Mitotane: White, crystalline powder, having a slight, aromatic odor. Soluble in alcohol, in ether, in solvent hexane, and in fixed oils and fats; practically insoluble in water.

Mitoxantrone Hydrochloride: Dark blue powder. Sparingly soluble in water; slightly soluble in methanol; practically insoluble in acetone, in acetonitrile, and in chloroform.

Modafinil: White to off-white, crystalline powder. Sparingly soluble in methanol; slightly soluble in absolute alcohol; very slightly soluble in water.

Mometasone Furoate: White to off-white powder. Melts at about 220°, with decomposition. Soluble in acetone and in methylene chloride.

Monensin Sodium: Off-white to tan, crystalline powder. Soluble in chloroform and in methanol; slightly soluble in water; practically insoluble in solvent hexane.

Mono- and Di-glycerides: Vary in consistency from yellow liquids, through ivory-colored plastics, to ivory white-colored solids (bead or flake forms). Soluble in alcohol, in ethyl acetate, in chloroform, and in other chlorinated hydrocarbons; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Monobenzene Ointment: Dispersible with, but not soluble in, water.

Monoethanolamine: Clear, colorless, moderately viscous liquid, having a distinctly ammoniacal odor. Miscible with water, with acetone, with alcohol, with glycerin, and with chloroform. Immiscible with ether, with solvent hexane, and with fixed oils, although it dissolves many essential oils. *NF category:* Emulsifying and/or solubilizing agent.

Monoglyceride Citrate: Soft white to ivory-colored, waxy solid with a lard-like consistency and bland odor. Dispersible in most common fat solvents and in alcohol. Insoluble in water.

Monosodium Glutamate: White, practically odorless, free-flowing crystals or crystalline powder. Freely soluble in water; sparingly soluble in alcohol. May have either a slightly sweet or a slightly salty taste. *NF category:* Flavors and perfumes.

Monothioglycerol: Colorless or pale yellow, viscous liquid, having a slight sulfidic odor. Is hygroscopic. Freely soluble in water; insoluble in ether. Miscible with alcohol. *NF category:* Antioxidant.

Montelukast Sodium: White or almost white, hygroscopic powder. Freely soluble to very soluble in alcohol; freely soluble in water and in methylene chloride.

Morantel Tartrate: A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate.

Moricizine Hydrochloride: White to off-white, crystalline powder. Melts at about 189°, with decomposition. Soluble in water and in alcohol.

Morphine Sulfate: White, feathery, silky crystals, cubical masses of crystals, or white, crystalline powder. Is odorless, and when exposed to air it gradually loses water of hydration. Darkens on prolonged exposure to light. Freely soluble in hot water; soluble in water; slightly soluble in alcohol but more so in hot alcohol; insoluble in chloroform and in ether.

Moxifloxacin Hydrochloride: Slightly yellow to yellow powder or crystals. Soluble in 0.1 N sodium hydroxide; sparingly soluble in water and in methanol; slightly soluble in 0.1 N hydrochloric acid, in dimethylformamide, and in

alcohol; practically insoluble in methylene chloride, in acetone, in ethyl acetate, and in toluene; insoluble in *tert*-butyl methyl ether and *n*-heptane.

Mumps Skin Test Antigen: Slightly turbid liquid.

Mumps Virus Vaccine Live: Solid having the characteristic appearance of substances dried from the frozen state. The Vaccine is to be constituted with a suitable diluent just prior to use. Constituted vaccine undergoes loss of potency on exposure to sunlight.

Mupirocin: White to off-white, crystalline solid. Freely soluble in acetone, in chloroform, in dehydrated alcohol, and in methanol; slightly soluble in ether; very slightly soluble in water.

Mycophenolate Mofetil: White or almost white, crystalline powder. Its melting range is between 94° and 98°. Freely soluble in acetone; soluble in methanol; sparingly soluble in dehydrated alcohol; slightly soluble in water.

Myristic Acid: Hard, white or faintly yellow, somewhat glossy, crystalline solid or white or yellow-white powder. Soluble in alcohol, in chloroform, and in ether; practically insoluble in water. *NF category:* Antifoaming agent.

Nabumetone: A white, or almost white, crystalline powder. Freely soluble in acetone; sparingly soluble in alcohol and in methanol; practically insoluble in water.

Nadolol: White to off-white, practically odorless, crystalline powder. Freely soluble in alcohol and in methanol; soluble in water at pH 2; slightly soluble in chloroform, in methylene chloride, in isopropyl alcohol, and in water (between pH 7 and pH 10); insoluble in acetone, in benzene, in ether, in hexane, and in trichloroethane.

Nafcillin Sodium: White to yellowish-white powder, having not more than a slight characteristic odor. Freely soluble in water and in chloroform; soluble in alcohol.

Nalidixic Acid: White to very pale yellow, odorless, crystalline powder. Soluble in chloroform, in methylene chloride, and in solutions of fixed alkali hydroxides and carbonates; slightly soluble in acetone, in alcohol, in methanol, and in toluene; very slightly soluble in ether and in water.

Naloxone Hydrochloride: White to slightly off-white powder. Its aqueous solution is acidic. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform.

Naloxone Hydrochloride Injection: Clear, colorless liquid.

Nandrolone Decanoate: Fine, white to creamy white, crystalline powder. Is odorless, or may have a slight odor. Soluble in chloroform, in alcohol, in acetone, and in vegetable oils; practically insoluble in water.

Naphazoline Hydrochloride: White, crystalline powder. Is odorless and has a bitter taste. Melts at a temperature of about 255°, with decomposition. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether.

Naproxen: White to off-white, practically odorless, crystalline powder. Soluble in chloroform, in dehydrated alcohol, and in alcohol; sparingly soluble in ether; practically insoluble in water.

Naproxen Sodium: White to creamy crystalline powder. Soluble in water and in methanol; sparingly soluble in alcohol; very slightly soluble in acetone; and practically insoluble in chloroform and in toluene. Melts at about 255°, with decomposition.

Narasin: White to off-white, crystalline powder. Melts at about 217°, with decomposition. Soluble in methanol and in water.

Naratriptan Hydrochloride: White to pale yellow solid. Soluble in water.

Natamycin: Off-white to cream-colored powder, which may contain up to 3 moles of water. Soluble in glacial acetic acid and in dimethylformamide; slightly soluble in methanol; practically insoluble in water.

Nateglinide: White powder. Freely soluble in methanol and in alcohol; soluble in ether; sparingly soluble in acetone and in octanol; practically insoluble in water.

Nefazodone Hydrochloride: Nonhygroscopic, white powder. Freely soluble in chloroform; soluble in propylene glycol; slightly soluble in polyethylene glycol and in water.

Neomycin Sulfate: White to slightly yellow powder, or cryodesiccated solid. Is odorless or practically so and is hygroscopic. Its solutions are dextrorotatory. Freely soluble in water; very slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether.

Netilmicin Sulfate: White to pale yellowish-white powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in ether.

Nevirapine: White to off-white, odorless to nearly odorless, crystalline powder. Slightly soluble in alcohol and in methanol; practically insoluble in water. Hydrous form also slightly soluble in propylene glycol.

Niacin: White crystals or crystalline powder. Is odorless, or has a slight odor. Melts at about 235°. Freely soluble in boiling water, in boiling alcohol, and in solutions of alkali hydroxides and carbonates; sparingly soluble in water; practically insoluble in ether.

Niacinamide: White, crystalline powder. Is odorless or practically so, and has a bitter taste. Its solutions are neutral to litmus. Freely soluble in water and in alcohol; soluble in glycerin.

Nifedipine: Yellow powder. Is affected by exposure to light. Freely soluble in acetone; practically insoluble in water.

Nimodipine: Light yellow or yellow, crystalline powder, affected by light. Freely soluble in ethyl acetate; sparingly soluble in alcohol; practically insoluble in water. Exhibits polymorphism.

Nitric Acid: Highly corrosive fuming liquid, having a characteristic, highly irritating odor. Stains animal tissues yellow. Boils at about 120°. Specific gravity is about 1.41. *NF category:* Acidifying agent.

Nitrofurantoin: Lemon-yellow, odorless crystals or fine powder. Has a bitter aftertaste. Soluble in dimethylformamide; very slightly soluble in water and in alcohol.

Nitrofurazone: Lemon yellow, odorless, crystalline powder. Darkens slowly on exposure to light. Melts at about 236°, with decomposition. Soluble in dimethylformamide; slightly soluble in propylene glycol and in polyethylene glycol mixtures; very slightly soluble in alcohol and in water; practically insoluble in chloroform and in ether.

Nitrofurazone Ointment: Yellow, opaque, and water-miscible, and has ointment-like consistency.

Nitrofurazone Topical Solution: Light yellow, clear, somewhat viscous liquid, having a faint characteristic odor. Miscible with water.

Nitrogen: Colorless, odorless, tasteless gas. Is nonflammable and does not support combustion. One L at 0° and at a pressure of 760 mm of mercury weighs about 1.251 g. One volume dissolves in about 65 volumes of water and in about 9 volumes of alcohol at 20° and at a pressure of 760 mm of mercury. *NF category:* Air displacement.

Diluted Nitroglycerin: When diluted with lactose, it is a white, odorless powder. When diluted with propylene glycol or alcohol, it is a clear, colorless, or pale yellow liquid. [NOTE—Undiluted nitroglycerin occurs as a white to pale yellow, thick, flammable, explosive liquid.] Undiluted nitroglycerin is soluble in methanol, in alcohol, in carbon disulfide, in acetone, in ethyl ether, in ethyl acetate, in glacial acetic acid, in benzene, in toluene, in nitrobenzene, in phenol, in chloroform, and in methylene chloride; slightly soluble in water.

Nitromersol: Brownish yellow to yellow granules or brownish yellow to yellow powder. Is odorless and tasteless and is affected by light. Soluble in solutions of alkalis and

of ammonia by opening of the anhydride ring and the formation of a salt; very slightly soluble in water, in alcohol, in acetone, and in ether.

Nitromersol Topical Solution: Clear, reddish-orange solution. Is affected by light.

Nitrous Oxide: Colorless gas, without appreciable odor or taste. One L at 0° and at a pressure of 760 mm of mercury weighs about 1.97 g. One volume dissolves in about 1.4 volumes of water at 20° and at a pressure of 760 mm of mercury. Freely soluble in alcohol; soluble in ether and in oils.

Nizatidine: Off-white to buff crystalline solid. Freely soluble in chloroform; soluble in methanol; sparingly soluble in water.

Nonoxynol 9: Clear, colorless to light yellow, viscous liquid. Soluble in water, in alcohol, and in corn oil. *NF category:* Wetting and/or solubilizing agent.

Norepinephrine Bitartrate: White or faintly gray, odorless, crystalline powder. Slowly darkens on exposure to air and light. Its solutions are acid to litmus, having a pH of about 3.5. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Melts between 98° and 104°, without previous drying of the specimen, the melt being turbid.

Norepinephrine Bitartrate Injection: Colorless or practically colorless liquid, gradually turning dark on exposure to air and light.

Norethindrone: White to creamy white, odorless, crystalline powder. Is stable in air. Soluble in chloroform and in dioxane; sparingly soluble in alcohol; slightly soluble in ether; practically insoluble in water.

Norethindrone Acetate: White to creamy white, odorless, crystalline powder. Very soluble in chloroform; freely soluble in dioxane; soluble in ether and in alcohol; practically insoluble in water.

Norfloxacin: White to pale yellow, crystalline powder. Sensitive to light and moisture. Freely soluble in acetic acid; sparingly soluble in chloroform; slightly soluble in acetone, in water, and in alcohol; very slightly soluble in methanol and in ethyl acetate; insoluble in ether.

Norgestimate: White to pale yellow powder. Very to freely soluble in methylene chloride; sparingly soluble in acetonitrile; insoluble in water.

Norgestrel: White or practically white, practically odorless, crystalline powder. Freely soluble in chloroform; sparingly soluble in alcohol; insoluble in water.

Nortriptyline Hydrochloride: White to off-white powder, having a slight, characteristic odor. Its solution (1 in 100) has a pH of about 5. Soluble in water and in chloroform; sparingly soluble in methanol; practically insoluble in ether, in benzene, and in most other organic solvents.

Noscapine: Fine, white or practically white, crystalline powder. Freely soluble in chloroform; soluble in acetone; slightly soluble in alcohol and in ether; practically insoluble in water.

Novobiocin Calcium: White or yellowish-white, odorless, crystalline powder. Freely soluble in alcohol and in methanol; sparingly soluble in acetone and in butyl acetate; slightly soluble in water and in ether; very slightly soluble in chloroform.

Novobiocin Sodium: White or yellowish-white, odorless, hygroscopic, crystalline powder. Freely soluble in water, in alcohol, in methanol, in glycerin, and in propylene glycol; slightly soluble in butyl acetate; practically insoluble in acetone, in chloroform, and in ether.

Nystatin: Yellow to light tan powder, having an odor suggestive of cereals. Is hygroscopic, and is affected by long exposure to light, heat, and air. Freely soluble in dimethylformamide and in dimethyl sulfoxide; sparingly to slightly soluble in methanol, in *n*-propyl alcohol, and in *n*-butyl al-

cohol; practically insoluble in water and in alcohol; insoluble in chloroform and in ether.

Octoxynol 9: Clear, pale yellow, viscous liquid, having a faint odor and a bitter taste. Soluble in benzene and in toluene; practically insoluble in solvent hexane. Miscible with water, with alcohol, and with acetone. *NF category:* Wetting and/or solubilizing agent.

Octyldodecanol: Clear water-white, free-flowing liquid. Soluble in alcohol and in ether; insoluble in water. *NF category:* Vehicle (oleaginous).

Octyl Methoxycinnamate: Pale yellow oil. Insoluble in water.

Oflloxacin: Pale yellowish-white to light yellowish-white crystals or crystalline powder. Sparingly soluble in chloroform; slightly soluble in alcohol, in methanol, and in water.

Hydrophilic Ointment: *NF category:* Ointment base.

White Ointment: *NF category:* Ointment base.

Yellow Ointment: *NF category:* Ointment base.

Olanzapine: A yellow crystalline solid. Soluble in *n*-propanol; sparingly soluble in acetonitrile; slightly soluble in methanol and in dehydrated alcohol; practically insoluble in water.

Oleic Acid: Colorless to pale yellow, oily liquid when freshly prepared, but on exposure to air it gradually absorbs oxygen and darkens. Has a characteristic, lard-like odor and taste. When strongly heated in air, it is decomposed with the production of acrid vapors. Practically insoluble in water. Miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils. *NF category:* Emulsifying and/or solubilizing agent.

Oleovitamin A and D: Yellow to red, oily liquid, practically odorless or having a fish-like odor, and having no rancid odor or taste. Is a clear liquid at temperatures exceeding 65°, and may crystallize on cooling. Is unstable in air and in light. Very soluble in ether and in chloroform; soluble in dehydrated alcohol and in vegetable oils; insoluble in water and in glycerin.

Oleovitamin A and D Capsules: The oil contained in Oleovitamin A and D Capsules is a yellow to red, oily liquid, practically odorless or having a fish-like odor, and having no rancid odor or taste. Is a clear liquid at temperatures exceeding 65°, and may crystallize on cooling. Is unstable in air and in light.

Oleoyle Polyoxylglycerides: Amber, oily liquids. May develop deposit after prolonged storage at 20°. Freely soluble in methylene chloride; practically insoluble but dispersible in water. *NF category:* Ointment base; solvent.

Oleyle Alcohol: Clear, colorless to light yellow, oily liquid. Has a faint characteristic odor and a bland taste. Soluble in alcohol, in ether, in isopropyl alcohol, and in light mineral oil; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent.

Oleyle Oleate: Clear, colorless to light yellow liquid. Has a faint characteristic odor. Slightly soluble in alcohol. Miscible with chloroform and with ether. *NF category:* Emollient; emulsifying and/or solubilizing agent.

Olive Oil: Pale yellow, or light greenish-yellow, oily liquid, having a slight, characteristic odor and taste, with a faintly acrid aftertaste. Slightly soluble in alcohol. Miscible with ether, with chloroform, and with carbon disulfide. *Specific gravity* (841): Between 0.910 and 0.915. *NF category:* Vehicle (oleaginous).

Olmesartan Medoxomil: White to off-white crystalline powder. Sparingly soluble in methanol; practically insoluble in water.

Olopatadine Hydrochloride: White crystalline powder. Very soluble in formic acid; sparingly soluble in water; very slightly soluble in dehydrated alcohol.

Omeprazole: White to off-white powder. Melts between 150° and 160°, with decomposition. Soluble in di-

chloromethane; sparingly soluble in methanol and in alcohol; very slightly soluble in water.

Omeprazole Magnesium: White to off-white powder. Sparingly soluble in methanol; slightly soluble in alcohol; very slightly soluble in water and in dichloromethane.

Ondansetron: White to off-white powder. Very soluble in acid solutions; sparingly soluble in water.

Ondansetron Hydrochloride: White to off-white powder. Soluble in methanol; sparingly soluble in water and in alcohol; slightly soluble in isopropyl alcohol and in dichloromethane; very slightly soluble in acetone, in chloroform, and in ethyl acetate.

Opium: Has a very characteristic odor and a very bitter taste.

Powdered Opium: Light brown or moderately yellowish-brown powder.

Orbifloxacin: White to pale yellow crystals or crystalline powder. Odorless. Soluble in acetic acid; very slightly soluble in methanol, in water, and in chloroform; practically insoluble in ethanol and in diethyl ether.

Orlistat: White to off-white fine powder or fine powder with lumps. Freely soluble in chloroform; very soluble in methanol and in alcohol; practically insoluble in water.

Orphenadrine Citrate: White, practically odorless, crystalline powder, having a bitter taste. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform, in benzene, and in ether.

Osetamivir Phosphate: White to off-white powder. Freely soluble in water; soluble in methanol, in dimethyl sulfoxide, and in propylene glycol; sparingly soluble in dimethylformamide; slightly soluble in alcohol; very slightly soluble in isopropyl alcohol and in polyethylene glycol 400; practically insoluble in acetonitrile, in acetone, in dichloromethane, and in *n*-hexane.

Oxacillin Sodium: Fine, white, crystalline powder, odorless or having a slight odor. Freely soluble in water, in methanol, and in dimethyl sulfoxide; slightly soluble in absolute alcohol, in chloroform, in pyridine, and in methyl acetate; insoluble in ethyl acetate, in ether, in benzene, and in ethylene chloride.

Oxacillin Sodium for Injection: Fine, white, crystalline powder, odorless or having a slight odor. Freely soluble in water, in methanol, and in dimethyl sulfoxide; slightly soluble in absolute alcohol, in chloroform, in pyridine, and in methyl acetate; insoluble in ethyl acetate, in ether, in benzene, and in ethylene chloride.

Oxaliplatin: White to off-white crystalline powder. Slightly soluble in water; very slightly soluble in methanol; practically insoluble in alcohol.

Oxandrolone: White, odorless, crystalline powder. Is stable in air, but darkens on exposure to light. Melts at about 225°. Freely soluble in chloroform; sparingly soluble in alcohol and in acetone; practically insoluble in water.

Oxaprozin: White to yellowish-white, crystalline powder.

Oxazepam: Creamy white to pale yellow powder. Is practically odorless. Slightly soluble in alcohol and in chloroform; very slightly soluble in ether; practically insoluble in water.

Oxcarbazepine: Light orange to creamish white or off-white powder. Soluble in acetic acid; sparingly soluble in chloroform; practically insoluble in water.

Oxfendazole: White or almost white powder. Slightly soluble in alcohol and in methylene chloride; practically insoluble in water.

Oxprenolol Hydrochloride: White, crystalline powder. Freely soluble in alcohol, in chloroform, and in water; sparingly soluble in acetone; practically insoluble in ether.

Oxtriphylline: White, crystalline powder, having an amine-like odor. A solution (1 in 100) has a pH of about

10.3. Freely soluble in water and in alcohol; very slightly soluble in chloroform.

Oxybenzone: Pale yellow powder. Freely soluble in alcohol and in toluene; practically insoluble in water.

Oxybutynin Chloride: White, crystalline, practically odorless powder. Very soluble in methanol and in chloroform; freely soluble in water and in alcohol; soluble in acetone; slightly soluble in ether; very slightly soluble in hexane.

Oxycodone Hydrochloride: White to off-white, hygroscopic crystals or powder. Is odorless. Soluble in water; slightly soluble in alcohol.

Oxygen: Colorless, odorless, tasteless gas, which supports combustion more energetically than does air. One L at 0° and at a pressure of 760 mm of mercury weighs about 1.429 g. One volume dissolves in about 32 volumes of water and in about 7 volumes of alcohol at 20° and at a pressure of 760 mm of mercury.

Oxymetazoline Hydrochloride: White to practically white, fine crystalline powder. Is hygroscopic. Melts at about 300°, with decomposition. Soluble in water and in alcohol; practically insoluble in benzene, in chloroform, and in ether.

Oxymetholone: White to creamy white, crystalline powder. Is odorless, and is stable in air. Freely soluble in chloroform; soluble in dioxane; sparingly soluble in alcohol; slightly soluble in ether; practically insoluble in water.

Oxymorphone Hydrochloride: White or slightly off-white, odorless powder. Darkens on exposure to light. Its aqueous solutions are slightly acidic. Freely soluble in water; sparingly soluble in alcohol and in ether.

Oxyquinoline Sulfate: Yellow powder. Melts at about 185°. Very soluble in water; freely soluble in methanol; slightly soluble in alcohol; practically insoluble in acetone and in ether. *NF category:* Complexing agent.

Oxytetracycline: Pale yellow to tan, odorless, crystalline powder. Is stable in air, but exposure to strong sunlight causes it to darken. It loses potency in solutions of pH below 2, and is rapidly destroyed by alkali hydroxide solutions. Freely soluble in 3 N hydrochloric acid and in alkaline solutions; sparingly soluble in alcohol; very slightly soluble in water.

Oxytetracycline Calcium: Yellow to light brown, crystalline powder. Insoluble in water.

Oxytetracycline Hydrochloride: Yellow, odorless, crystalline powder, having a bitter taste. Is hygroscopic. Decomposes at a temperature exceeding 180°, and exposure to strong sunlight or to temperatures exceeding 90° in moist air causes it to darken. Its potency is diminished in solutions having a pH below 2, and is rapidly destroyed by alkali hydroxide solutions. Freely soluble in water, but crystals of oxytetracycline base separate as a result of partial hydrolysis of the hydrochloride; sparingly soluble in alcohol and in methanol, and even less soluble in dehydrated alcohol; insoluble in chloroform and in ether.

Paclitaxel: White to off-white powder. Soluble in alcohol; insoluble in water.

Padimate O: A light yellow, mobile liquid having a faint, aromatic odor. Soluble in alcohol, in isopropyl alcohol, and in mineral oil; practically insoluble in water, in glycerin, and in propylene glycol.

Palm Oil: White to yellowish, fatty solid to semisolid. Insoluble in water. *NF category:* Coating agent; emulsifying and/or solubilizing agent.

Hydrogenated Palm Oil: White to yellowish, fatty solid to semi-solid. Freely soluble in ether; very slightly soluble in alcohol; practically insoluble in water. *NF category:* Coating agent; tablet binder; tablet and/or capsule lubricant.

Palm Kernel Oil: White to yellowish, fatty solid. Insoluble in water. *NF category:* Coating agent; emulsifying and/or solubilizing agent.

Palmitic Acid: Hard, white or faintly yellow, somewhat glossy crystalline solid, or white or yellowish-white powder. It has a slight characteristic odor and taste. Soluble in alcohol, in ether, and in chloroform; practically insoluble in water.

Pamidronate Disodium: White, crystalline powder. Soluble in water and in 2 N sodium hydroxide; sparingly soluble in 0.1 N hydrochloric acid and in 0.1 N acetic acid; practically insoluble in organic solvents.

Pancreatin: Cream-colored, amorphous powder, having a faint, characteristic, but not offensive odor. It hydrolyzes fats to glycerol and fatty acids, changes protein into proteoses and derived substances, and converts starch into dextrins and sugars. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action.

Pancrelipase: Cream-colored, amorphous powder, having a faint, characteristic, but not offensive odor. Pancrelipase hydrolyzes fats to glycerol and fatty acids, changes protein into proteoses and derived substances, and converts starch into dextrins and sugars. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action.

Pancrelipase Capsules: The contents of Capsules conform to the *Description* under *Pancrelipase*, except that the odor may vary with the flavoring agent used.

Pancuronium Bromide: White, yellowish-white, or slightly pink, crystalline powder. Is hygroscopic. Freely soluble in water, in methylene chloride, and in alcohol.

Panthenol: White to creamy white, crystalline powder having a slight, characteristic odor. Freely soluble in water, in alcohol, and in propylene glycol; soluble in chloroform and in ether; slightly soluble in glycerin.

Pantoprazole Sodium: White to off-white powder. Freely soluble in water, in methanol, and in dehydrated alcohol; practically insoluble in hexane and in dichloromethane.

Papain: White to light tan, amorphous powder. Soluble in water, the solution being colorless to light yellow and more or less opalescent; practically insoluble in alcohol, in chloroform, and in ether.

Papaverine Hydrochloride: White crystals or white, crystalline powder. Is odorless, and has a slightly bitter taste. Is optically inactive. Its solutions are acid to litmus. Melts at about 220°, with decomposition. Soluble in water and in chloroform; slightly soluble in alcohol; practically insoluble in ether.

Parachlorophenol: White or pink crystals having a characteristic phenolic odor. When undiluted, it whitens and cauterizes the skin and mucous membranes. Melts at about 42°. Very soluble in alcohol, in glycerin, in chloroform, in ether, and in fixed and volatile oils; soluble in petrolatum; sparingly soluble in water and in liquid petrolatum.

Paraffin: Colorless or white, more or less translucent mass showing a crystalline structure. Is odorless and tasteless, and is slightly greasy to the touch. Freely soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils; slightly soluble in dehydrated alcohol; insoluble in water and in alcohol. *NF category:* Stiffening agent.

Synthetic Paraffin: Very hard, white, practically tasteless and odorless wax. Contains mostly long-chain, unbranched, saturated hydrocarbons, with a small amount of branched hydrocarbons. Is represented by the formula C_nH_{2n+2} , in which n may range from 20 to about 100. The average molecular weight may range from 400 to 1400. Slightly soluble in aromatic and normal paraffinic solvents; very slightly soluble in aliphatic, oxygenated, and halogenated hydrocarbon solvents; insoluble in water. *NF category:* Stiffening agent.

Paraldehyde: Colorless, transparent liquid. Has a strong, characteristic but not unpleasant or pungent odor, and a disagreeable taste. Specific gravity is about 0.99. Soluble in water, but less soluble in boiling water. Miscible with alcohol, with chloroform, with ether, and with volatile oils.

Paricalcitol: White to almost white powder. Soluble in alcohol; insoluble in water.

Paromomycin Sulfate: Creamy white to light yellow powder. Is odorless or practically odorless, and is very hygroscopic. Very soluble in water; insoluble in alcohol, in chloroform, and in ether.

Paroxetine Hydrochloride: White to off-white solid. Soluble in methanol and in alcohol; slightly soluble in water.

Peanut Oil: Colorless or pale yellow, oily liquid with a bland taste. May have a characteristic, nutty odor. Very slightly soluble in alcohol. Miscible with ether, with chloroform, and with carbon disulfide. *Specific gravity* (841): Between 0.912 and 0.920. *Refractive index* (831): Between 1.462 and 1.464 at 40°. *NF category:* Solvent; vehicle (oleaginous).

Pectin: Coarse or fine powder, yellowish-white in color, almost odorless, and having a mucilaginous taste. Soluble in 20 parts of water, forming a viscous, opalescent, colloidal solution that flows readily and is acid to litmus; practically insoluble in alcohol or in diluted alcohol and in other organic solvents. Pectin dissolves in water more readily if first moistened with alcohol, glycerin, or simple syrup, or if first mixed with 3 or more parts of sucrose. *NF category:* Suspending and/or viscosity-increasing agent.

Penbutolol Sulfate: White to off-white, crystalline powder. Melts at about 217°, with decomposition. Soluble in water and in methanol.

Penicillamine: White or practically white, crystalline powder, having a slight, characteristic odor. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether.

Penicillin G Benzathine: White, odorless, crystalline powder. Sparingly soluble in alcohol; very slightly soluble in water.

Penicillin G Potassium: Colorless or white crystals, or white, crystalline powder. Is odorless or practically so, and is moderately hygroscopic. Its solutions are dextrorotatory. Its solutions retain substantially full potency for several days at temperatures below 15°, but are rapidly inactivated by acids, by alkali hydroxides, by glycerin, and by oxidizing agents. Very soluble in water, in saline TS, and in dextrose solutions; sparingly soluble in alcohol.

Penicillin G Procaine: White crystals or white, very fine, microcrystalline powder. Is odorless or practically odorless, and is relatively stable in air. Its solutions are dextrorotatory. Is rapidly inactivated by acids, by alkali hydroxides, and by oxidizing agents. Soluble in alcohol and in chloroform; slightly soluble in water.

Penicillin G Sodium: Colorless or white crystals or white to slightly yellow, crystalline powder. Is odorless or practically odorless, and is moderately hygroscopic. Its solutions are dextrorotatory. Is relatively stable in air, but is inactivated by prolonged heating at about 100°, especially in the presence of moisture. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15°. Its solutions are rapidly inactivated by acids, by alkali hydroxides, by oxidizing agents, and by penicillinase.

Penicillin V: White, odorless, crystalline powder. Freely soluble in alcohol and in acetone; very slightly soluble in water; insoluble in fixed oils.

Penicillin V Benzathine: Practically white powder, having a characteristic odor. Sparingly soluble in chloroform; slightly soluble in alcohol and in ether; very slightly soluble in water.

Penicillin V Potassium: White, odorless, crystalline powder. Very soluble in water; slightly soluble in alcohol; insoluble in acetone.

Pentamidine Isethionate: White or almost white powder or colorless crystals, hygroscopic. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in methylene chloride.

Pentazocine: White or very pale, tan-colored powder. Freely soluble in chloroform; soluble in alcohol, in acetone, and in ether; sparingly soluble in benzene and in ethyl acetate; practically insoluble in water.

Pentazocine Hydrochloride: White, crystalline powder. It exhibits polymorphism, one form melting at about 254° and the other at about 218°. Freely soluble in chloroform; soluble in alcohol; sparingly soluble in water; very slightly soluble in acetone and in ether; practically insoluble in benzene.

Pentetic Acid: White, odorless or almost odorless powder. Melts with foaming and degradation at 220°.

Pentobarbital: White to practically white, fine, practically odorless powder. May occur in a polymorphic form that melts at about 116°. This form gradually reverts to the more stable higher-melting form upon being heated at about 110°. Very soluble in alcohol, in methanol, in ether, in chloroform, and in acetone; soluble in benzene; very slightly soluble in water and in carbon tetrachloride.

Pentobarbital Sodium: White, crystalline granules or white powder. Is odorless or has a slight characteristic odor, and has a slightly bitter taste. Its solutions decompose on standing, heat accelerating the decomposition. Very soluble in water; freely soluble in alcohol; practically insoluble in ether.

Pentoxifylline: White to almost white crystalline powder. Freely soluble in chloroform and in methanol; soluble in water; sparingly soluble in alcohol; slightly soluble in ether.

Peppermint: Has an aromatic, characteristic odor and a pungent taste, and produces a cooling sensation in the mouth. *NF category:* Flavors and perfumes.

Peppermint Oil: Colorless or pale yellow liquid, having a strong, penetrating, characteristic odor and a pungent taste, followed by a sensation of cold when air is drawn into the mouth. *NF category:* Flavors and perfumes.

Peppermint Spirit: A clear, colorless liquid with a peppermint fragrance. Freely soluble in methanol and in diethyl ether; soluble in water. *NF category:* Flavors and perfumes.

Peppermint Water: *NF category:* Vehicle (flavored and/or sweetened).

Perflubron: Clear, colorless, practically odorless liquid.

Pergolide Mesylate: White to off-white powder. Sparingly soluble in methanol; slightly soluble in water, in dehydrated alcohol, and in chloroform; very slightly soluble in acetone; practically insoluble in ether.

Perphenazine: White to creamy white, odorless powder. Freely soluble in alcohol and in chloroform; soluble in acetone; practically insoluble in water.

Pertussis Immune Globulin: Transparent or slightly opalescent liquid, practically colorless, free from turbidity or particles, and practically odorless. May develop a slight, granular deposit during storage. Is standardized for agglutinating activity with the U.S. Standard Antipertussis Serum.

Petrolatum: Unctuous yellowish to light amber mass, having not more than a slight fluorescence even after being melted. Is transparent in thin layers. Is free or practically free from odor and taste. Freely soluble in benzene, in carbon disulfide, in chloroform, and in turpentine oil; soluble in ether, in solvent hexane, and in most fixed and volatile oils; practically insoluble in cold and hot alcohol and in cold dehydrated alcohol; insoluble in water. *NF category:* Ointment base.

Hydrophilic Petrolatum: *NF category:* Ointment base.

White Petrolatum: White or faintly yellowish, unctuous mass, transparent in thin layers even after cooling to 0°. Freely soluble in benzene, in carbon disulfide, and in chloroform; soluble in ether, in solvent hexane, and in most fixed and volatile oils; slightly soluble in cold or hot alcohol, and in cold dehydrated alcohol; insoluble in water. *NF category:* Ointment base.

Phenazopyridine Hydrochloride: Light or dark red to dark violet, crystalline powder. Is odorless, or has a slight odor. Melts at about 235°, with decomposition. Slightly soluble in water, in alcohol, and in chloroform.

Phendimetrazine Tartrate: White, odorless, crystalline powder. Freely soluble in water; sparingly soluble in warm alcohol; insoluble in chloroform, in acetone, in ether, and in benzene. Phendimetrazine base is extracted by organic solvents from alkaline solution.

Phenelzine Sulfate: White to yellowish white powder, having a characteristic odor. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether.

Pheniramine Maleate: White, crystalline powder having a faint amine-like odor. Soluble in water and in alcohol.

Phenmetrazine Hydrochloride: White to off-white, crystalline powder. Very soluble in water; freely soluble in alcohol and in chloroform.

Phenobarbital: White, odorless, glistening, small crystals, or white, crystalline powder, which may exhibit polymorphism. Is stable in air. Its saturated solution has a pH of about 5. Soluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates; sparingly soluble in chloroform; very slightly soluble in water.

Phenobarbital Sodium: Flaky crystals, or white, crystalline granules, or white powder. Is odorless, has a bitter taste, and is hygroscopic. Its solutions are alkaline to phenolphthalein TS, and decompose on standing. Very soluble in water; soluble in alcohol; practically insoluble in ether and in chloroform.

Phenol: Colorless to light pink, interlaced or separate, needle-shaped crystals, or white to light pink, crystalline mass. Has a characteristic odor. Is liquefied by warming and by the addition of 10% of water. Boils at about 182°, and its vapor is flammable. Gradually darkens on exposure to light and air. Very soluble in alcohol, in glycerin, in chloroform, in ether, and in fixed and volatile oils; soluble in water; sparingly soluble in mineral oil. *NF category:* Antimicrobial preservative.

Liquefied Phenol: Colorless to pink liquid, which may develop a red tint upon exposure to air or light. Has a characteristic, somewhat aromatic odor. It whitens and cauterizes the skin and mucous membranes. Specific gravity is about 1.065. Miscible with alcohol, with ether, and with glycerin. A mixture of equal volumes of Liquefied Phenol and glycerin is miscible with water.

Camphorated Phenol Topical Gel: Clear, colorless, oily gel.

Phenolsulfonphthalein: A bright-red to dark-red, crystalline powder. Slightly soluble in alcohol; very slightly soluble in water.

Phenoxyethanol: A colorless, slightly viscous liquid. Slightly soluble in water, in peanut oil, and in olive oil. Miscible with acetone, with alcohol, and with glycerol. *NF category:* Antimicrobial preservative.

Phensuximide: White to off-white, crystalline powder. Is odorless, or has not more than a slight odor. Very soluble in chloroform; soluble in alcohol; slightly soluble in water.

Phentermine Hydrochloride: White, odorless, hygroscopic, crystalline powder. Soluble in water and in the lower alcohols; slightly soluble in chloroform; insoluble in ether.

Phentolamine Mesylate: White or off-white, odorless, crystalline powder. Its solutions are acid to litmus, having a pH of about 5, and slowly deteriorate. Melts at about 178°.

Freely soluble in water and in alcohol; slightly soluble in chloroform.

Phenylalanine: White, odorless crystals, having a slightly bitter taste. Sparingly soluble in water; very slightly soluble in methanol, in alcohol, and in dilute mineral acids.

Phenylbenzimidazole Sulfonic Acid: White to ivory-colored, odorless powder. Soluble in alcohol; practically insoluble in oily solvents and in water. Its salts are freely soluble in water.

Phenylbutazone: White to off-white, odorless, crystalline powder. Freely soluble in acetone and in ether; soluble in alcohol; very slightly soluble in water.

Phenylephrine Bitartrate: White or almost white powder or colorless crystals. Freely soluble in water.

Phenylephrine Hydrochloride: White or practically white, odorless crystals, having a bitter taste. Freely soluble in water and in alcohol.

Phenylephrine Hydrochloride Nasal Solution: Clear, colorless or slightly yellow, odorless liquid. Is neutral or acid to litmus.

Phenylephrine Hydrochloride Ophthalmic Solution: Clear, colorless or slightly yellow liquid, depending on the concentration.

Phenylethyl Alcohol: Colorless liquid, having a rose-like odor and a sharp, burning taste. Very soluble in alcohol, in fixed oils, in glycerin, and in propylene glycol; sparingly soluble in water; slightly soluble in mineral oil. *NF category:* Antimicrobial preservative.

Phenylmercuric Acetate: White to creamy white, crystalline powder, or small white prisms or leaflets. Is odorless. Soluble in alcohol and in acetone; slightly soluble in water. *NF category:* Antimicrobial preservative.

Phenylmercuric Nitrate: White, crystalline powder. Is affected by light. Its saturated solution is acid to litmus. Slightly soluble in alcohol and in glycerin; very slightly soluble in water. It is more soluble in the presence of either nitric acid or alkali hydroxides. *NF category:* Antimicrobial preservative.

Phenylpropanolamine Bitartrate: White, crystalline powder.

Phenylpropanolamine Hydrochloride: White, crystalline powder, having a slight aromatic odor. Is affected by light. Freely soluble in water and in alcohol; insoluble in ether.

Phenyltoloxamine Citrate: White, crystalline powder. Very soluble in boiling water; slightly soluble in cold water and in alcohol; practically insoluble in cold acetone, in ethyl ether, and in toluene.

Phenytol: White, odorless powder. Melts at about 295°. Soluble in hot alcohol; slightly soluble in cold alcohol, in chloroform, and in ether; practically insoluble in water.

Phenytol Sodium: White, odorless powder. Is somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide. Freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbon dioxide; soluble in alcohol; practically insoluble in ether and in chloroform.

Sodium Phosphate P 32 Solution: Clear, colorless solution. Upon standing, both the Solution and the glass container may darken as a result of the effects of the radiation.

Phosphoric Acid: Colorless, odorless liquid of syrupy consistency. Specific gravity is about 1.71. Miscible with water and with alcohol. *NF category:* Acidifying agent; buffering agent.

Diluted Phosphoric Acid: Clear, colorless, odorless liquid. Specific gravity is about 1.057. *NF category:* Acidifying agent.

Physostigmine: White, odorless, microcrystalline powder. Acquires a red tint when exposed to heat, light, air, or contact with traces of metals. Melts at a temperature not

lower than 103°. Very soluble in chloroform and in dichloromethane; freely soluble in alcohol; soluble in benzene and in fixed oils; slightly soluble in water.

Physostigmine Salicylate: White, shining, odorless crystals or white powder. Acquires a red tint when exposed to heat, light, air, or contact with traces of metals for long periods. Melts at about 184°. Freely soluble in chloroform; soluble in alcohol; sparingly soluble in water; slightly soluble in ether.

Physostigmine Sulfate: White, odorless, microcrystalline powder. Is deliquescent in moist air and acquires a red tint when exposed to heat, light, air, or contact with traces of metals for long periods. Melts at about 143°. Freely soluble in water; very soluble in alcohol; very slightly soluble in ether.

Phytonadione: Clear, yellow to amber, very viscous, odorless or practically odorless liquid, having a specific gravity of about 0.967. Is stable in air, but decomposes on exposure to sunlight. Soluble in dehydrated alcohol, in benzene, in chloroform, in ether, and in vegetable oils; slightly soluble in alcohol; insoluble in water.

Pilocarpine: A viscous, oily liquid, or crystals melting at about 34°. Exceedingly hygroscopic. Soluble in water, in alcohol, and in chloroform; sparingly soluble in ether and in benzene; practically insoluble in petroleum ether.

Pilocarpine Hydrochloride: Colorless, translucent, odorless, faintly bitter crystals. Is hygroscopic and is affected by light. Its solutions are acid to litmus. Very soluble in water; freely soluble in alcohol; slightly soluble in chloroform; insoluble in ether.

Pilocarpine Nitrate: Shining, white crystals. Is stable in air but is affected by light. Its solutions are acid to litmus. Freely soluble in water; sparingly soluble in alcohol; insoluble in chloroform and in ether.

Pimozide: White, crystalline powder. Freely soluble in chloroform; slightly soluble in ether and in alcohol; insoluble in water.

Pindolol: White to off-white, crystalline powder, having a faint odor. Slightly soluble in methanol; very slightly soluble in chloroform; practically insoluble in water.

Pioglitazone Hydrochloride: White crystals or crystalline powder. Soluble in dimethylformamide; slightly soluble in dehydrated alcohol; very slightly soluble in acetone and in acetonitrile; practically insoluble in water; insoluble in ether.

Piperacillin: White to off-white, crystalline powder. Very soluble in methanol; slightly soluble in isopropyl alcohol; very slightly soluble in ethyl acetate and in water.

Piperacillin Sodium: White to off-white solid. Freely soluble in water and in alcohol.

Piperazine: White to slightly off-white lumps or flakes, having an ammoniacal odor. Soluble in water and in alcohol; insoluble in ether.

Piperazine Adipate: White crystalline powder. Soluble in water; practically insoluble in alcohol.

Piperazine Citrate: White, crystalline powder, having not more than a slight odor. Its solution (1 in 10) has a pH of about 5. Soluble in water; insoluble in alcohol and in ether.

Piperazine Dihydrochloride: White crystalline powder. Soluble in water.

Piperazine Phosphate: White crystalline powder. Sparingly soluble in water; practically insoluble in alcohol.

Piroxicam: Off-white to light tan or light yellow, odorless powder. Forms a monohydrate that is yellow. Slightly soluble in alcohol and in aqueous alkaline solutions; very slightly soluble in water, in dilute acids, and in most organic solvents.

Plantago Seed: All varieties are practically odorless and have a bland, mucilaginous taste.

Plicamycin: Yellow, odorless, hygroscopic, crystalline powder. Freely soluble in ethyl acetate; slightly soluble in water and in methanol; very slightly soluble in alcohol.

Podophyllum: Has a slight odor and a disagreeably bitter and acrid taste.

Podophyllum Resin: Amorphous powder, varying in color from light brown to greenish yellow, turning darker when subjected to a temperature exceeding 25° or when exposed to light. Has a slight, peculiar, faintly bitter taste. Its alcohol solution is acid to moistened litmus paper. Soluble in alcohol with a slight opalescence; partially soluble in ether and in chloroform.

Polacrilin Potassium: White to off-white, free-flowing powder. Has a faint odor or is odorless. Insoluble in water and in most liquids. *NF category:* Tablet disintegrant.

Poliovirus Vaccine Inactivated: Clear, reddish-tinged or yellowish liquid, that may have a slight odor because of the preservative.

Poloxalene: Colorless or pale yellow liquid. Soluble in water, in chloroform, and in ethylene dichloride.

Poloxamer: *NF category:* Emulsifying and/or solubilizing agent; wetting and/or solubilizing agent.

Poloxamer 124: Colorless liquid, having a mild odor. When solidified, it melts at about 16°. Freely soluble in water, in alcohol, in isopropyl alcohol, in propylene glycol, and in xylene.

Poloxamer 188: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about 52°. Freely soluble in water and in alcohol.

Poloxamer 237: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about 49°. Freely soluble in water and in alcohol; sparingly soluble in isopropyl alcohol and in xylene.

Poloxamer 338: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about 57°. Freely soluble in water and in alcohol; sparingly soluble in propylene glycol.

Poloxamer 407: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about 56°. Freely soluble in water, in alcohol, and in isopropyl alcohol.

Polycarbophil: White to creamy white granules, having a characteristic, ester-like odor. Swells in water to a range of volumes, depending primarily on the pH. Insoluble in water, in dilute acids, in dilute alkalies, and in common organic solvents.

Hydrogenated Polydecene: Clear, colorless, odorless, tasteless liquid. Very slightly soluble in water. *NF category:* Emollient; ointment base; solvent; vehicle (oleaginous).

Polydextrose: Off-white to light tan-colored solid. Very soluble in water; soluble in alcohol; slightly soluble in glycerin and in propylene glycol. *NF category:* Bulking agent; humectant.

Hydrogenated Polydextrose: Off-white to light tan-colored solid. Very soluble in water; soluble in alcohol; slightly soluble in glycerin and in propylene glycol. *NF category:* Bulking agent; coating agent; humectant; tablet binder; suspending and/or viscosity-increasing agent.

Polyethylene Glycol: Polyethylene Glycol is usually designated by a number that corresponds approximately to its average molecular weight. As the average molecular weight increases, the water solubility, vapor pressure, hygroscopicity, and solubility in organic solvents decrease, while congealing temperature, specific gravity, flash point, and viscosity increase. Liquid grades occur as clear to slightly hazy, colorless or practically colorless, slightly hygroscopic, viscous liquids, having a slight, characteristic odor, and a specific gravity at 25° of about 1.12. Solid grades occur as practically odorless and tasteless, white, waxy, plastic material having a consistency similar to beeswax, or as creamy white flakes, beads, or powders. The accompanying table states the approximate congealing temperatures that are characteristic of commonly available grades. Liquid grades are miscible with water; solid grades are freely soluble in water;

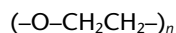
and all are soluble in acetone, in alcohol, in chloroform, in ethylene glycol monoethyl ether, in ethyl acetate, and in toluene; all are insoluble in ether and in hexane. *NF category*: Coating agent; plasticizer; solvent; suppository base; tablet and/or capsule lubricant.

Nominal Molecular Weight Polyethylene Glycol	Approximate Congealing Temperature (°)
300	–11
400	6
600	20
900	34
1000	38
1450	44
3350	56
4500	58
8000	60

Polyethylene Glycol Monomethyl Ether: Polyethylene Glycol Monomethyl Ether is usually designated by a number that corresponds approximately to its average molecular weight. As the average molecular weight increases, the water solubility, vapor pressure, hygroscopicity, and solubility in organic solvents decrease, while congealing temperature, specific gravity, flash point, and viscosity increase. Liquid grades occur as clear to slightly hazy, colorless or practically colorless, slightly hygroscopic, viscous liquids, having a slight, characteristic odor, and a specific gravity at 25° of about 1.09 – 1.10. Solid grades occur as practically odorless and tasteless, white, waxy, plastic material having a consistency similar to beeswax, or as creamy white flakes, beads, or powders. The accompanying table states the approximate congealing temperatures that are characteristic of commonly available grades. Liquid grades are miscible with water; solid grades are freely soluble in water; and all are soluble in acetone, in alcohol, in chloroform, in ethylene glycol monoethyl ether, in ethyl acetate, and in toluene; all are insoluble in ether and in hexane. *NF category*: Ointment base; solvent; plasticizer.

Nominal Molecular Weight Polyethylene Glycol Monomethyl Ether	Approximate Congealing Temperature (°)
350	–7
550	17
750	28
1000	35
2000	51
5000	59
8000	60
10000	61

Polyethylene Oxide: Polyethylene oxide resins are high molecular weight polymers having the common structure:



in which n , the degree of polymerization, varies from about 2000 to over 100,000. Polyethylene oxide, being a polyether, strongly hydrogen bonds with water. It is nonionic and undergoes salting-out effects associated with neutral molecules in solutions of high dielectric media. Salting-out effects manifest themselves in depressing the upper temperature limit of solubility, and in reducing the viscosity of both dilute and concentrated solutions of the polymers. All molecular weight grades are powdered or granular solids. They are soluble in water but, because of the high solution viscosities obtained (see *table*), solutions over 1% in water may be difficult to prepare. The water solubility, hygroscopicity, solubility in organic solvents, and melting point do not vary in

the specified molecular weight range. At room temperature polyethylene oxide is miscible with water in all proportions. At concentrations of about 20% polymer in water, the solutions are nontacky, reversible, elastic gels. At higher concentrations, the solutions are tough, elastic materials with the water acting as a plasticizer. Polyethylene oxide is also freely soluble in acetonitrile, in ethylene dichloride, in trichloroethylene, and in methylene chloride. Heating may be required to obtain solutions in many other organic solvents. It is insoluble in aliphatic hydrocarbons, in ethylene glycol, in diethylene glycol, and in glycerol. *NF category*: Suspending and/or viscosity-increasing agent; tablet binder.

Approximate Molecular Weight	Typical Solution Viscosity (cps), 25°	
	5% Solution	1% Solution
100,000	40	
200,000	100	
300,000	800	
400,000	3000	
600,000	6000	
900,000	15,000	
4,000,000		3500
5,000,000		5500

Polyethylene 50 Stearate: *NF category*: Emulsifying and/or solubilizing agent.

Polyglyceryl 3 Diisostearate: Viscous liquid. Soluble in alcohol, in methylene chloride, in mineral oil, and in vegetable oils; insoluble in water. *NF category*: Emulsifying and/or solubilizing agent; ointment base.

Polyglyceryl Dioleate: Viscous liquid. Soluble in methylene chloride, in mineral oil, and in vegetable oils; sparingly soluble in alcohol; insoluble in water. *NF category*: Emulsifying and/or solubilizing agent.

Polyisobutylene: Low molecular-weight grades are soft and gummy; high molecular-weight grades are tough and elastic. All grades are light in color, odorless, and tasteless. Soluble in diisobutylene, in toluene, and in chloroform; insoluble in water.

Polymyxin B Sulfate: White to buff-colored powder. Is odorless or has a faint odor. Freely soluble in water; slightly soluble in alcohol.

Polyoxyl Lauryl Ether: A material with 3–5 oxyethylene units per molecule is a colorless liquid. Soluble or dispersible in alcohol; practically insoluble in water and in hexane. A material with 9–23 oxyethylene units per molecule is a white, waxy mass. Soluble or dispersible in water; soluble in alcohol; practically insoluble in hexane. *NF category*: Emulsifying and/or solubilizing agent.

Polyoxyl Oleate: A slightly yellowish, viscous liquid. Dispersible in water and in oils. Soluble in alcohol and in isopropyl alcohol. Miscible with fatty oils and with waxes. Its refractive index is about 1.466.

Polyoxyl 10 Oleyl Ether: White, soft semisolid, or pale yellow liquid, having a bland odor. Soluble in water and in alcohol. Dispersible in mineral oil and in propylene glycol, with possible separation on standing. *NF category*: Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polyoxyl 15 Hydroxystearate: Yellowish to white waxy mass. Very soluble in water; soluble in alcohol and in 2-propanol; insoluble in mineral oil. It solidifies at 25°. *NF category*: Tablet and/or capsule lubricant; wetting and/or solubilizing agent; vehicle (oleaginous).

Polyoxyl 20 Cetostearyl Ether: Cream-colored, waxy, unctuous mass, melting, when heated, to a clear brownish-yellow liquid. Soluble in water, in alcohol, and in acetone; insoluble in solvent hexane. *NF category*: Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polyoxyl 35 Castor Oil: Yellow, oily liquid, having a faint, characteristic odor and a somewhat bitter taste. Very soluble in water, producing a practically odorless and colorless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polyoxyl 40 Hydrogenated Castor Oil: White to yellowish paste or pasty liquid, having a faint odor and a slight taste. Very soluble in water, producing a practically tasteless, odorless, and colorless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polyoxyl 40 Stearate: Waxy, white to light tan solid. Is odorless or has a faint, fat-like odor. Soluble in water, in alcohol, in ether, and in acetone; insoluble in mineral oil and in vegetable oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polyoxyl Stearate: White or slightly yellowish waxy mass. Soluble in alcohol and in isopropyl alcohol. Polyoxyl stearate corresponding to a product with 6–8 units of ethylene oxide per molecule is soluble in fatty oils and in waxes; practically insoluble in water. Polyoxyl stearate corresponding to a product with 20–100 units of ethylene oxide per molecule is soluble in water; practically insoluble in fatty oils and in waxes. *NF category:* Emulsifying and/or solubilizing agent; wetting and/or solubilizing agent.

Polyoxyl Stearyl Ether: A white to yellowish-white, waxy, unctuous mass, pellets, microbeads, or flakes. Polyoxyl Stearyl Ether with 2 oxyethylene units per molecule is soluble in alcohol, with heating, and in methylene chloride; practically insoluble in water. Polyoxyl Stearyl Ether with 10 oxyethylene units per molecule is soluble in water and in alcohol. Polyoxyl Stearyl Ether with 20 oxyethylene units per molecule is soluble in water, in alcohol, and in methylene chloride. After melting, it solidifies at about 45°.

Polysorbate 20: Lemon to amber liquid having a faint characteristic odor. Soluble in water, in alcohol, in ethyl acetate, in methanol, and in dioxane; insoluble in mineral oil. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polysorbate 40: Yellow liquid having a faint, characteristic odor. Soluble in water and in alcohol; insoluble in mineral oil and in vegetable oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polysorbate 60: Lemon- to orange-colored, oily liquid or semi-gel having a faint, characteristic odor. Soluble in water, in ethyl acetate, and in toluene; insoluble in mineral oil and in vegetable oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polysorbate 80: Lemon- to amber-colored, oily liquid having a faint, characteristic odor and a warm, somewhat bitter taste. Very soluble in water, producing an odorless and practically colorless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oil. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Polyvinyl Acetate: White or off-white powder or colorless granules or beads. Freely soluble in ethyl acetate; soluble in alcohol, in acetone, and in chloroform; practically insoluble in water. It is hygroscopic and swells in water. *NF category:* Coating agent; desiccant; tablet binder.

Polyvinyl Acetate Dispersion: Opaque, white or off-white, slightly viscous liquid. Miscible with water and with ethanol. It is sensitive to spoilage by microbial contaminants. *NF category:* Coating agent.

Polyvinyl Acetate Phthalate: Free-flowing white powder. May have a slight odor of acetic acid. Soluble in metha-

nol and in alcohol; insoluble in water, in methylene chloride, and in chloroform. *NF category:* Coating agent.

Polyvinyl Alcohol: White to cream-colored granules, or white to cream-colored powder. Is odorless. Freely soluble in water at room temperature. Solution may be effected more rapidly at somewhat higher temperatures. *NF category:* Suspending and/or viscosity-increasing agent.

Sulfurated Potash: Irregular, liver-brown pieces when freshly made, changing to a greenish yellow. Has an odor of hydrogen sulfide and a bitter, acrid, and alkaline taste, and decomposes on exposure to air. A solution (1 in 10) is light brown in color and is alkaline to litmus. Freely soluble in water, usually leaving a slight residue. Alcohol dissolves only the sulfides.

Potassium Acetate: Colorless, monoclinic crystals or white, crystalline powder having a saline and slightly alkaline taste. Is odorless, or has a faint acetous odor. Deliquesces on exposure to moist air. Very soluble in water; freely soluble in alcohol.

Potassium Alginate: White to yellow, fibrous or granular powder. Dissolves in water to form a viscous, colloidal solution; insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than 30% by weight; insoluble in chloroform, in ether, and in acids having a pH lower than about 3.

Potassium Benzoate: White, odorless, or practically odorless, granular or crystalline powder. Is stable in air. Freely soluble in water; soluble in 90% alcohol; sparingly soluble in alcohol. *NF category:* Antimicrobial preservative.

Potassium Bicarbonate: Colorless, transparent, monoclinic prisms or as a white, granular powder. Is odorless, and is stable in air. Its solutions are neutral or alkaline to phenolphthalein TS. Freely soluble in water; practically insoluble in alcohol.

Potassium Bitartrate: Colorless or slightly opaque crystals, or white, crystalline powder. A saturated solution is acid to litmus. Soluble in boiling water; slightly soluble in water; very slightly soluble in alcohol.

Potassium Bromide: White, crystalline powder or colorless, cubical crystals. Freely soluble in water and in glycerol; slightly soluble in alcohol.

Potassium Chloride: Colorless, elongated, prismatic, or cubical crystals, or white, granular powder. Is odorless, has a saline taste, and is stable in air. Its solutions are neutral to litmus. Freely soluble in water; insoluble in alcohol. *NF category:* Tonicity agent.

Potassium Citrate: Transparent crystals or white, granular powder. Is odorless, has a cooling, saline taste, and is deliquescent when exposed to moist air. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Buffering agent.

Potassium Gluconate: White to yellowish-white, crystalline powder or granules. Is odorless, has a slightly bitter taste, and is stable in air. Its solutions are slightly alkaline to litmus. Freely soluble in water; practically insoluble in dehydrated alcohol, in ether, in benzene, and in chloroform.

Potassium Hydroxide: White or practically white, fused masses, or small pellets, or flakes, or sticks, or other forms. Is hard and brittle and shows a crystalline fracture. Exposed to air, it rapidly absorbs carbon dioxide and moisture, and deliquesces. Very soluble in boiling alcohol; freely soluble in water, in alcohol, and in glycerin. *NF category:* Alkalizing agent.

Potassium Iodide: Hexahedral crystals, either transparent and colorless or somewhat opaque and white, or a white, granular powder. Is slightly hygroscopic. Its solutions are neutral or alkaline to litmus. Very soluble in water and even more soluble in boiling water; freely soluble in glycerin; soluble in alcohol.

Potassium Iodide Oral Solution: Clear, colorless, odorless liquid, having a characteristic, strongly salty taste. Is neutral or alkaline to litmus. Specific gravity is about 1.70.

Potassium Metabisulfite: White or colorless, free-flowing crystals, crystalline powder, or granules, usually having an odor of sulfur dioxide. Gradually oxidizes in air to the sulfate. Its solutions are acid to litmus. Soluble in water; insoluble in alcohol. *NF category:* Antioxidant.

Potassium Metaphosphate: White, odorless powder. Soluble in dilute solutions of sodium salts; insoluble in water. *NF category:* Buffering agent.

Potassium Nitrate: White, crystalline powder or colorless crystals. Very soluble in boiling water; freely soluble in water; soluble in glycerin; practically insoluble in alcohol.

Potassium Permanganate: Dark purple crystals, almost opaque by transmitted light and of a blue metallic luster by reflected light. Its color is sometimes modified by a dark bronze-like appearance. Is stable in air. Freely soluble in boiling water; soluble in water.

Dibasic Potassium Phosphate: Colorless or white, somewhat hygroscopic, granular powder. The pH of a solution (1 in 20) is about 8.5 to 9.6. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Buffering agent.

Monobasic Potassium Phosphate: Colorless crystals or white, granular or crystalline powder. Is odorless, and is stable in air. The pH of a solution (1 in 100) is about 4.5. Freely soluble in water; practically insoluble in alcohol. *NF category:* Buffering agent.

Potassium Sodium Tartrate: Colorless crystals or white, crystalline powder, having a cooling, saline taste. As it effloresces slightly in warm, dry air, the crystals are often coated with a white powder. Freely soluble in water; practically insoluble in alcohol.

Potassium Sorbate: White crystals or powder, having a characteristic odor. Melts at about 270°, with decomposition. Freely soluble in water; soluble in alcohol. *NF category:* Antimicrobial preservative.

Povidone: White to slightly creamy white powder. Is hygroscopic. Freely soluble in water, in methanol, and in alcohol; slightly soluble in acetone; practically insoluble in ether. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder.

Povidone-Iodine: Yellowish-brown to reddish-brown, amorphous powder, having a slight, characteristic odor. Its solution is acid to litmus. Soluble in water and in alcohol; practically insoluble in chloroform, in carbon tetrachloride, in ether, in solvent hexane, and in acetone.

Povidone-Iodine Topical Aerosol Solution: The liquid obtained from Povidone-Iodine Topical Aerosol Solution is transparent, having a reddish brown color.

Pralidoxime Chloride: White to pale-yellow, crystalline powder. Is odorless and is stable in air. Freely soluble in water.

Pramipexole Dihydrochloride: White to almost white crystalline powder. Freely soluble in water; soluble in methanol; slightly soluble in alcohol; practically insoluble in methylene chloride.

Pramoxine Hydrochloride: White to practically white, crystalline powder, having a numbing taste. May have a slight aromatic odor. The pH of a solution (1 in 100) is about 4.5. Freely soluble in water and in alcohol; soluble in chloroform; very slightly soluble in ether.

Pravastatin Sodium: White to yellowish white, hygroscopic powder. Freely soluble in water and in methanol; soluble in dehydrated alcohol; practically insoluble in acetonitrile and in chloroform.

Praziquantel: White or practically white, crystalline powder; odorless or having a faint characteristic odor. Freely soluble in alcohol and in chloroform; very slightly soluble in water.

Prazosin Hydrochloride: White to tan powder. Slightly soluble in water, in methanol, in dimethylformamide, and in dimethylacetamide; very slightly soluble in alcohol; practically insoluble in chloroform and in acetone.

Prednicarbate: White to almost white, crystalline powder. Freely soluble in acetone and in alcohol; sparingly soluble in propylene glycol; practically insoluble in water.

Prednisolone: White to practically white, odorless, crystalline powder. Melts at about 235°, with some decomposition (see *Melting Range or Temperature* (741)). Soluble in methanol and in dioxane; sparingly soluble in acetone and in alcohol; slightly soluble in chloroform; very slightly soluble in water.

Prednisolone Acetate: White to practically white, odorless, crystalline powder. Melts at about 235°, with some decomposition (see *Melting Range or Temperature* (741)). Slightly soluble in acetone, in alcohol, and in chloroform; practically insoluble in water.

Prednisolone Hemisuccinate: Fine, creamy white powder with friable lumps; practically odorless. Melts at about 205°, with decomposition. Freely soluble in alcohol; soluble in acetone; very slightly soluble in water.

Prednisolone Sodium Phosphate: White or slightly yellow, friable granules or powder. Is odorless or has a slight odor. Is slightly hygroscopic. Freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone and in dioxane.

Prednisolone Sodium Succinate for Injection: Creamy white powder with friable lumps, having a slight odor.

Prednisolone Tebutate: White to slightly yellow, free-flowing powder, which may show some soft lumps. Is odorless or has not more than a moderate, characteristic odor. Is hygroscopic. Freely soluble in chloroform and in dioxane; soluble in acetone; sparingly soluble in alcohol and in methanol; very slightly soluble in water.

Prednisone: White to practically white, odorless, crystalline powder. Melts at about 230°, with some decomposition (see *Melting Range or Temperature* (741)). Slightly soluble in alcohol, in chloroform, in dioxane, and in methanol; very slightly soluble in water.

Prilocaine: White or almost white powder or crystal aggregates. Very soluble in alcohol and in acetone; slightly soluble in water.

Prilocaine Hydrochloride: White, odorless, crystalline powder, having a bitter taste. Freely soluble in water and in alcohol; slightly soluble in chloroform; very slightly soluble in acetone; practically insoluble in ether.

Primaquine Phosphate: Orange-red, crystalline powder. Is odorless and has a bitter taste. Its solutions are acid to litmus. Melts at about 200°. Soluble in water; insoluble in chloroform and in ether.

Primidone: White, crystalline powder. Is odorless and has a slightly bitter taste. Slightly soluble in alcohol; very slightly soluble in water and in most organic solvents.

Probucol: White to off-white, crystalline powder. Freely soluble in chloroform and in *n*-propyl alcohol; soluble in alcohol and in solvent hexane; insoluble in water.

Probenecid: White or practically white, fine, crystalline powder. Is practically odorless. Soluble in dilute alkali, in chloroform, in alcohol, and in acetone; practically insoluble in water and in dilute acids.

Procainamide Hydrochloride: White to tan, crystalline powder. Is odorless. Its solution (1 in 10) has a pH between 5 and 6.5. Very soluble in water; soluble in alcohol; slightly soluble in chloroform; very slightly soluble in benzene and in ether.

Procainamide Hydrochloride Injection: Colorless, or having not more than a slight yellow color.

Procaine Hydrochloride: Small, white crystals or white, crystalline powder. Is odorless. Exhibits local anesthetic properties when placed on the tongue. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform; practically insoluble in ether.

Procaine Hydrochloride Injection: Clear, colorless liquid.

Prochlorperazine: Clear, pale yellow, viscous liquid. Is sensitive to light. Freely soluble in alcohol, in chloroform, and in ether; very slightly soluble in water.

Prochlorperazine Edisylate: White to very light yellow, odorless, crystalline powder. Its solutions are acid to litmus. Freely soluble in water; very slightly soluble in alcohol; insoluble in ether and in chloroform.

Prochlorperazine Maleate: White or pale yellow, practically odorless, crystalline powder. Its saturated solution is acid to litmus. Slightly soluble in warm chloroform; practically insoluble in water and in alcohol.

Procyclidine Hydrochloride: White, crystalline powder, having a moderate, characteristic odor. Melts at about 225°, with decomposition. Soluble in water and in alcohol; insoluble in ether and in acetone.

Progesterone: White or creamy white, odorless, crystalline powder. Is stable in air. Soluble in alcohol, in acetone, and in dioxane; sparingly soluble in vegetable oils; practically insoluble in water.

Proguanil Hydrochloride: White, crystalline powder. Sparingly soluble in alcohol; slightly soluble in water; practically insoluble in methylene chloride.

Proline: White, odorless crystals, having a slightly sweet taste. Freely soluble in water and in absolute alcohol; insoluble in ether, in butanol, and in isopropanol.

Promazine Hydrochloride: White to slightly yellow, practically odorless, crystalline powder. It oxidizes upon prolonged exposure to air and acquires a blue or pink color. Freely soluble in water and in chloroform.

Promethazine Hydrochloride: White to faint yellow, practically odorless, crystalline powder. Slowly oxidizes, and acquires a blue color, on prolonged exposure to air. Freely soluble in water, in hot dehydrated alcohol, and in chloroform; practically insoluble in ether, in acetone, and in ethyl acetate.

Propafenone Hydrochloride: White powder. Soluble in methanol and in hot water; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone; insoluble in diethyl ether and in toluene.

Propane: Colorless, flammable gas (boiling temperature is about –42°). One hundred volumes of water dissolves 6.5 volumes at 17.8° and 753 mm pressure; 100 volumes of anhydrous alcohol dissolves 790 volumes at 16.6° and 754 mm pressure; 100 volumes of ether dissolves 926 volumes at 16.6° and 757 mm pressure; 100 volumes of chloroform dissolves 1299 volumes at 21.6° and 757 mm pressure. Vapor pressure at 21° is about 10290 mm of mercury (108 psig). *NF category:* Aerosol propellant.

Add the following:

■**Propanediol:** Clear, colorless, hygroscopic liquid. *Specific Gravity* (841), *Method I:* 1.040–1.065. Soluble in water, in alcohol, in methyl alcohol, in isopropyl alcohol, in butyl alcohol, in acetone, in propylene glycol, and miscible with many polar solvents. *NF category:* Humectant; solvent; wetting and/or solubilizing agent. ■ *US (NF31)*

Propantheline Bromide: White or practically white crystals. Is odorless and has a bitter taste. Melts at about 160°, with decomposition. Very soluble in water, in alcohol, and in chloroform; practically insoluble in ether and in benzene.

Proparacaine Hydrochloride: White to off-white, or faintly buff-colored, odorless, crystalline powder. Its solutions are neutral to litmus. Soluble in water, in warm alcohol, and in methanol; insoluble in ether and in benzene.

Proparacaine Hydrochloride Ophthalmic Solution: Colorless or faint yellow solution.

Propionic Acid: Oily liquid having a slight pungent, rancid odor. Miscible with water and with alcohol and various other organic solvents. *NF category:* Acidifying agent.

Propofol: Clear, colorless to slightly yellowish liquid. Very soluble in methanol and in ethanol; slightly soluble in cyclohexane and in isopropyl alcohol; very slightly soluble in water.

Propoxycaine Hydrochloride: White, odorless, crystalline solid, which discolors on prolonged exposure to light and air. The pH of a solution (1 in 50) is about 5.4. Freely soluble in water; soluble in alcohol; sparingly soluble in ether; practically insoluble in acetone and in chloroform.

Propoxyphene Hydrochloride: White, crystalline powder. Is odorless, and has a bitter taste. Freely soluble in water; soluble in alcohol, in chloroform, and in acetone; practically insoluble in benzene and in ether.

Propoxyphene Napsylate: White powder, having essentially no odor, but having a bitter taste. Soluble in methanol, in alcohol, in chloroform, and in acetone; very slightly soluble in water.

Propranolol Hydrochloride: White to off-white, crystalline powder. Is odorless and has a bitter taste. Melts at about 164°. Soluble in water and in alcohol; slightly soluble in chloroform; practically insoluble in ether.

Propyl Gallate: White, crystalline powder having a very slight, characteristic odor. Freely soluble in alcohol; slightly soluble in water. *NF category:* Antioxidant.

Propylene Glycol: Clear, colorless, viscous liquid having a slight, characteristic taste. Is practically odorless. Absorbs moisture when exposed to moist air. Miscible with water, with acetone, and with chloroform. Soluble in ether and will dissolve many essential oils, but is immiscible with fixed oils. *NF category:* Humectant; plasticizer; solvent.

Propylene Glycol Alginate: White to yellowish fibrous or granular powder. Practically odorless and tasteless. Soluble in water, in solutions of dilute organic acids, and, depending on the degree of esterification, in hydroalcoholic mixture containing up to 60% by weight of alcohol to form stable, viscous colloidal solutions at a pH of 3. *NF category:* Suspending and/or viscosity-increasing agent.

Propylene Glycol Dicaprylate/Dicaprate: Clear, colorless or slightly yellow oily liquid at 20°. Soluble in fatty oils and in light petroleum; slightly soluble in dehydrated alcohol; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; vehicle.

Propylene Glycol Dilaurate: Clear, oily liquid at 20°. Colorless or slightly yellow. Very soluble in alcohol, in methanol, and in methylene chloride; practically insoluble in water.

Propylene Glycol Monocaprylate: Clear, colorless, or slightly yellow, oily liquid at 20°. Very soluble in alcohol, in chloroform, and in methylene chloride; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule diluent; vehicle.

Propylene Glycol Monolaurate: Clear, oily liquid at 20°. Colorless or slightly yellow. Very soluble in alcohol, in methanol, and in methylene chloride; practically insoluble in water.

Propylene Glycol Monostearate: White, wax-like solid or as white, wax-like beads or flakes. Has a slight, agreeable, fatty odor and taste. Soluble in organic solvents such as alcohol, mineral or fixed oils, benzene, ether, and acetone; insoluble in water, but may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent. *NF category:* Emulsifying and/or solubilizing agent.

Propylhexedrine: Clear, colorless liquid, having a characteristic, amine-like odor. Volatilizes slowly at room temperature. Absorbs carbon dioxide from the air, and its solutions are alkaline to litmus. Boils at about 205°. Very slightly soluble in water. Miscible with alcohol, with chloroform, and with ether.

Propylidone: White or almost white, crystalline powder. Is odorless or has a faint odor. Soluble in acetone, in alcohol, and in ether; practically insoluble in water.

Propylparaben: Small, colorless crystals or white powder. Freely soluble in alcohol and in ether; slightly soluble in boiling water; very slightly soluble in water. *NF category:* Antimicrobial preservative.

Propylparaben Sodium: White powder. Is odorless and hygroscopic. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. *NF category:* Antimicrobial preservative.

Propylthiouracil: White, powdery, crystalline substance. Is starch-like in appearance and to the touch, and has a bitter taste. Soluble in ammonium hydroxide and in alkali hydroxides; sparingly soluble in alcohol; slightly soluble in water, in chloroform, and in ether.

Protamine Sulfate Injection: Colorless solution, which may have the odor of a preservative.

Protamine Sulfate for Injection: White, odorless powder, having the characteristic appearance of solids dried from the frozen state.

Protein Hydrolysate Injection: Yellowish to reddish-amber, transparent liquid.

Protriptyline Hydrochloride: White to yellowish powder. Is odorless, or has not more than a slight odor. Melts at about 168°. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether.

Pseudoephedrine Hydrochloride: Fine, white to off-white crystals or powder, having a faint characteristic odor. Very soluble in water; freely soluble in alcohol; slightly soluble in chloroform.

Pseudoephedrine Sulfate: White crystals or crystalline powder. Is odorless. Freely soluble in alcohol.

Pullulan: White powder. Freely soluble in water; practically insoluble in dehydrated alcohol. *NF category:* Bulking agent for freeze-drying; coating agent; plasticizer; polymer membrane; sequestering agent; suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant; wetting and/or solubilizing agent.

Pumice: Very light, hard, rough, porous, grayish masses or gritty, grayish powder. Is odorless and tasteless, and is stable in air. Practically insoluble in water; is not attacked by acids.

Pyrantel Pamoate: Yellow to tan solid. Soluble in dimethyl sulfoxide; slightly soluble in dimethylformamide; practically insoluble in water and in methanol.

Pyrazinamide: White to practically white, odorless or practically odorless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol, in ether, and in chloroform.

Pyrethrum Extract: Pale yellow liquid having a bland, flowery odor. Soluble in mineral oil and in most organic solvents; insoluble in water. *Pyrethrins I* denotes the group containing pyrethrin 1, cinerin 1, and jasmolin 1; *Pyrethrins II* denotes the group containing pyrethrin 2, cinerin 2, and jasmolin 2.

Pyridostigmine Bromide: White or practically white, crystalline powder, having an agreeable, characteristic odor. Is hygroscopic. Freely soluble in water, in alcohol, and in chloroform; slightly soluble in solvent hexane; practically insoluble in ether.

Pyridoxine Hydrochloride: White to practically white crystals or crystalline powder. Is stable in air, and is slowly affected by sunlight. Its solutions have a pH of about 3. Freely soluble in water; slightly soluble in alcohol; insoluble in ether.

Pyrilamine Maleate: White, crystalline powder, usually having a faint odor. Its solutions are acid to litmus. Very soluble in water; freely soluble in alcohol and in chloroform; slightly soluble in ether and in benzene.

Pyrimethamine: White, odorless, crystalline powder. Slightly soluble in acetone, in alcohol, and in chloroform; practically insoluble in water.

Pyrvinium Pamoate: Bright orange or orange-red to practically black, crystalline powder. Freely soluble in glacial acetic acid; slightly soluble in chloroform and in methoxyethanol; very slightly soluble in methanol; practically insoluble in water and in ether.

Pyrvinium Pamoate Oral Suspension: Dark red, opaque suspension of essentially very fine, amorphous particles or aggregates, usually less than 10 µm in size. Larger particles, some of which may be crystals, up to 100 µm in size also may be present.

Quazepam: Off-white to yellowish powder.

Quinapril Hydrochloride: White to off-white powder, with a pink cast at times. Freely soluble in aqueous solvents.

Quinidine Gluconate: White powder. Is odorless and has a very bitter taste. Freely soluble in water; slightly soluble in alcohol.

Quinidine Sulfate: Fine, needle-like, white crystals, frequently cohering in masses, or fine, white powder. Is odorless, and darkens on exposure to light. Its solutions are neutral or alkaline to litmus. Soluble in alcohol; sparingly soluble in chloroform; slightly soluble in water; insoluble in ether.

Quinine Sulfate: White, fine, needle-like crystals, usually lusterless, making a light and readily compressible mass. Is odorless. It darkens on exposure to light. Its saturated solution is neutral or alkaline to litmus. Freely soluble in alcohol at 80°, and in a mixture of 2 volumes of chloroform and 1 volume of dehydrated alcohol; sparingly soluble in water at 100°; slightly soluble in water, in alcohol, and in chloroform; very slightly soluble in ether.

Rabies Immune Globulin: Transparent or slightly opalescent liquid, practically colorless and practically odorless. May develop a slight, granular deposit during storage.

Rabies Vaccine: White to straw-colored, amorphous pellet, which may or may not become fragmented when shaken.

Racemethionine: Almost white, crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. It melts at about 270°. *NF category:* Antioxidant; buffering agent; flavors and perfumes.

Racpinephrine: White to nearly white, crystalline, odorless powder, gradually darkening on exposure to light and air. With acids, it forms salts that are readily soluble in water, and the base may be recovered by the addition of ammonium hydroxide. Very slightly soluble in water and in alcohol; insoluble in ether, in chloroform, and in fixed and volatile oils.

Racpinephrine Hydrochloride: Fine, white, odorless powder. Darkens on exposure to light and air. Its solutions are acid to litmus. Melts at about 157°. Freely soluble in water; sparingly soluble in alcohol.

Raloxifene Hydrochloride: Almost white to pale yellow powder. Freely soluble in dimethylsulfoxide; sparingly soluble in methanol; slightly soluble in alcohol; very slightly soluble in water, in isopropyl alcohol, and in octanol; practically insoluble in ether and in ethyl acetate.

Ramipril: White to almost white crystalline powder. Freely soluble in methanol; sparingly soluble in water.

Ranitidine Hydrochloride: White to pale yellow, crystalline, practically odorless powder. Is sensitive to light and moisture. Melts at about 140°, with decomposition. Very soluble in water; sparingly soluble in alcohol.

Fully Hydrogenated Rapeseed Oil: White, waxy solid. Insoluble in water and in alcohol. *NF category:* Coating agent; stiffening agent.

Superglycerinated Fully Hydrogenated Rapeseed Oil: White solid. Insoluble in water and in alcohol. *NF category:* Coating agent; emulsifying and/or solubilizing agent; stiffening agent.

Purified Rayon: White, lustrous or dull, fine, soft, filamentous fibers, appearing under the microscope as round, oval, or slightly flattened translucent rods, straight or crimped, striate and with serrate cross-sectional edges. Is practically odorless and practically tasteless. Very soluble in ammoniated cupric oxide TS and in dilute sulfuric acid (3 in 5); insoluble in ordinary solvents.

Repaglinide: White to off-white solid. Melts at about 132° to 136°. Soluble in methanol.

Reserpine: White or pale buff to slightly yellowish, odorless, crystalline powder. Darkens slowly on exposure to light, but more rapidly when in solution. Freely soluble in acetic acid and in chloroform; slightly soluble in benzene; very slightly soluble in alcohol and in ether; insoluble in water.

Resorcinol: White, or practically white, needle-shaped crystals or powder. Has a faint, characteristic odor and a sweetish, followed by a bitter, taste. Acquires a pink tint on exposure to light and air. Its solution (1 in 20) is neutral or acid to litmus. Freely soluble in water, in alcohol, in glycerin, and in ether; slightly soluble in chloroform.

Ribavirin: White, crystalline powder. Freely soluble in water; slightly soluble in dehydrated alcohol.

Riboflavin: Yellow to orange-yellow, crystalline powder having a slight odor. Melts at about 280°. Its saturated solution is neutral to litmus. When dry, it is not appreciably affected by diffused light, but when in solution, light induces quite rapid deterioration, especially in the presence of alkalies. Soluble in dilute solutions of alkalies; very slightly soluble in water, in alcohol, and in isotonic sodium chloride solution; insoluble in ether and in chloroform.

Riboflavin 5'-Phosphate Sodium: Fine, orange-yellow, crystalline powder, having a slight odor. Sparingly soluble in water. When dry, it is not affected by diffused light, but when in solution, light induces deterioration rapidly. Is hygroscopic.

Rifabutin: Amorphous red-violet powder. Soluble in chloroform and in methanol; sparingly soluble in alcohol; very slightly soluble in water.

Rifampin: Red-brown, crystalline powder. Freely soluble in chloroform; soluble in ethyl acetate and in methanol; very slightly soluble in water.

Riluzole: White to slightly yellow powder or crystalline powder. Freely soluble in acetonitrile, in alcohol, and in methylene chloride; slightly soluble in hexane; very slightly soluble in water.

Rimexolone: White to off-white powder. Freely soluble in chloroform; sparingly soluble in methanol.

Risedronate Sodium: White to off-white powder. Soluble in water and in aqueous solutions; insoluble in common organic solvents.

Risperidone: White or almost white powder. Soluble in methylene chloride; sparingly soluble in alcohol; practically insoluble in water.

Ritodrine Hydrochloride: White to nearly white, odorless or practically odorless, crystalline powder. Melts at about 200°. Freely soluble in water and in alcohol; soluble in *n*-propyl alcohol; practically insoluble in ether.

Ritonavir: White to light tan powder. Freely soluble in methanol and in methylene chloride; very slightly soluble in acetonitrile; practically insoluble in water.

Rivastigmine Tartrate: White to off-white powder. Very soluble in water and in methanol; very slightly soluble in ethyl acetate.

Rizatriptan Benzoate: White to almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; slightly soluble in methylene chloride.

Rocuronium Bromide: Almost white or pale yellow. Slightly hygroscopic powder. Freely soluble in water and in dehydrated alcohol.

Ropinirole Hydrochloride: Pale cream to yellow powder. Soluble in water.

Ropivacaine Hydrochloride: White, crystalline powder. Soluble in water.

Rose Oil: Colorless or yellow liquid, having the characteristic odor and taste of rose. At 25° is a viscous liquid. Upon gradual cooling, changes to a translucent, crystalline mass, easily liquefied by warming. *NF category:* Flavors and perfumes.

Rose Water Ointment: *NF category:* Ointment base.

Stronger Rose Water: Practically colorless and clear, having the pleasant odor and taste of fresh rose blossoms. Is free from empyreuma, mustiness, and fungal growths. *NF category:* Flavors and perfumes.

Change to read:

Rosiglitazone Maleate: White to off-white solid. ^{▲▲USP36} Sparingly soluble in alcohol; slightly soluble in methylene chloride; practically insoluble to very slightly soluble in water.

Roxarsone: Pale yellow, crystalline powder. Freely soluble in acetic acid, in acetone, in alkalies, in methanol, and in dehydrated alcohol; soluble in boiling water; sparingly soluble in dilute mineral acids; slightly soluble in cold water; insoluble in ether and in ethyl acetate. Puffs up and deflagrates on heating.

Rubella Virus Vaccine Live: Solid having the characteristic appearance of substances dried from the frozen state. Undergoes loss of potency on exposure to sunlight. The Vaccine is to be constituted with a suitable diluent just prior to use.

Add the following:

▲Rufinamide: White, crystalline neutral powder. Slightly soluble in tetrahydrofuran and in methanol; very slightly soluble in alcohol and in acetonitrile; practically insoluble in water. ^{▲USP36}

Saccharin: White crystals or white, crystalline powder. Is odorless or has a faint, aromatic odor. In dilute solution, it is intensely sweet. Its solutions are acid to litmus. Soluble in boiling water; sparingly soluble in alcohol; slightly soluble in water, in chloroform, and in ether. Is readily dissolved by dilute solutions of ammonia, by solutions of alkali hydroxides, and by solutions of alkali carbonates with the evolution of carbon dioxide. *NF category:* Sweetening agent.

Saccharin Calcium: White crystals or white, crystalline powder. Is odorless, or has a faint, aromatic odor, and has an intensely sweet taste even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. Freely soluble in water. *NF category:* Sweetening agent.

Saccharin Sodium: White crystals or white, crystalline powder. Is odorless, or has a faint, aromatic odor, and has an intensely sweet taste even in dilute solutions. Its dilute solution is about 300 times as sweet as sucrose. When in powdered form, it usually contains about one-third the theoretical amount of water of hydration as a result of efflorescence. Freely soluble in water; sparingly soluble in alcohol. *NF category:* Sweetening agent.

Saccharin Sodium Oral Solution: Clear, colorless, odorless liquid, having a sweet taste.

Safflower Oil: Light yellow oil. Thickens and becomes rancid on prolonged exposure to air. Insoluble in water. Miscible with ether and with chloroform. *NF category:* Vehicle (oleaginous).

Salicylamide: White, practically odorless, crystalline powder. Freely soluble in ether and in solutions of alkalies; soluble in alcohol and in propylene glycol; slightly soluble in water and in chloroform.

Salicylic Acid: White crystals, usually in fine needles, or fluffy, white, crystalline powder. Has a sweetish, followed by an acrid, taste and is stable in air. The synthetic form is white and odorless. When prepared from natural methyl salicylate, it may have a slightly yellow or pink tint, and a faint, mint-like odor. Freely soluble in alcohol and in ether; soluble in boiling water; sparingly soluble in chloroform; slightly soluble in water and in benzene.

Salmeterol Xinafoate: White to off-white powder. Soluble in methanol; slightly soluble in alcohol, in isopropanol, and in chloroform; practically insoluble in water (pH 8), and in saline solution (0.9% w/w).

Scopolamine Hydrobromide: Colorless or white crystals or white, granular powder. Melts at about 197°, with decomposition. Is odorless, and slightly efflorescent in dry air. Freely soluble in water; soluble in alcohol; slightly soluble in chloroform; insoluble in ether.

Secobarbital: White, amorphous or crystalline, odorless powder, having a slightly bitter taste. Its saturated solution has a pH of about 5.6. Freely soluble in alcohol, in ether, and in solutions of fixed alkali hydroxides and carbonates; soluble in chloroform; very slightly soluble in water.

Secobarbital Sodium: White powder. Is odorless, has a bitter taste, and is hygroscopic. Its solutions decompose on standing, heat accelerating the decomposition. Very soluble in water; soluble in alcohol; practically insoluble in ether.

Selegiline Hydrochloride: White, odorless, crystalline powder. Freely soluble in water, in chloroform, and in methanol.

Selenium Sulfide: Reddish-brown to bright orange powder, having not more than a faint odor. Practically insoluble in water and in organic solvents.

Sennosides: Brownish powder.

Serine: White, odorless crystals, having a sweet taste. Soluble in water; practically insoluble in absolute alcohol and in ether.

Sertraline Hydrochloride: White or off-white crystalline powder. Sparingly soluble in absolute alcohol; slightly soluble in water, in acetone, and in isopropanol.

Sesame Oil: Pale yellow, oily liquid. Is practically odorless, and has a bland taste. Slightly soluble in alcohol. Miscible with ether, with chloroform, with solvent hexane, and with carbon disulfide. *NF category:* Solvent, vehicle (oleaginous).

Sevoflurane: Clear, colorless, volatile, nonflammable liquid. Slightly soluble in water. Miscible with alcohol, with chloroform, and with ether.

Shellac: *Orange Shellac*—Thin, hard, brittle, transparent, pale lemon-yellow to brownish orange flakes, having little or no odor; *Bleached Shellac*—Opaque, amorphous cream to yellow granules or coarse powder, having little or no odor. Soluble (very slowly) in alcohol, 85% to 95% (w/w), in ether, 13% to 15%, in benzene, 10% to 20%, in petroleum ether, 2% to 6%; soluble in aqueous solutions of ethanamines, alkalies, and borax; sparingly soluble in oil of turpentine; insoluble in water. *NF category:* Coating agent.

Sibutramine Hydrochloride Monohydrate: White to cream crystalline powder. Slightly soluble in pH 5.2 water.

Sildenafil Citrate: White or almost white slightly hygroscopic crystalline powder. Slightly soluble in water and in methanol; practically insoluble in hexane.

Dental-Type Silica: Fine, white, hygroscopic, odorless, amorphous powder, in which the diameter of the average particles ranges between 0.5 and 40 μm . Soluble in hot solutions of alkali hydroxides; insoluble in water, in alcohol, and in acid (except hydrofluoric acid). *NF category:* Glidant and/or anticaking agent; suspending and/or viscosity-increasing agent.

Hydrophobic Colloidal Silica: Light, fine, white or almost white, amorphous powder, not wettable by water. Dissolves slowly in hot solutions of alkali hydroxides. Practically

insoluble in water and in mineral acids, except hydrofluoric acid. *NF category:* Glidant and/or anticaking agent; suspending and/or viscosity-increasing agent.

Purified Siliceous Earth: Very fine, white, light gray, or pale buff mixture of amorphous powder and lesser amounts of crystalline polymorphs, including quartz and cristobalite. Is gritty, readily absorbs moisture, and retains about four times its weight of water without becoming fluid. Insoluble in water, in acids, and in dilute solutions of the alkali hydroxides. *NF category:* Filtering aid; sorbent.

Silicon Dioxide: Fine, white, hygroscopic, odorless, amorphous powder, in which the diameter of the average particles ranges between 2 and 10 μm . Soluble in hot solutions of alkali hydroxides; insoluble in water, in alcohol, and in other organic solvents. *NF category:* Desiccant; suspending and/or viscosity-increasing agent.

Colloidal Silicon Dioxide: Light, white, nongritty powder of extremely fine particle size (about 15 nm). Soluble in hot solutions of alkali hydroxides; insoluble in water and in acid (except hydrofluoric). *NF category:* Glidant and/or anticaking agent; suspending and/or viscosity-increasing agent.

Silver Nitrate: Colorless or white crystals. The pH of its solutions is about 5.5. On exposure to light in the presence of organic matter, it becomes gray or grayish black. Very soluble in water and even more so in boiling water; freely soluble in boiling alcohol; sparingly soluble in alcohol; slightly soluble in ether.

Toughened Silver Nitrate: White, crystalline masses generally molded as pencils or cones. It breaks with a fibrous fracture. Its solutions are neutral to litmus. It becomes gray or grayish black upon exposure to light. Soluble in water to the extent of its nitrate content (there is always a residue of silver chloride); partially soluble in alcohol; slightly soluble in ether.

Simethicone: Translucent, gray, viscous fluid. The liquid phase is soluble in chloroform, in ether, and in benzene, but silicon dioxide remains as a residue in these solvents. Insoluble in water and in alcohol. *NF category:* Antifoaming agent; water repelling agent.

Simvastatin: White to off-white powder. Freely soluble in chloroform, in methanol, and in alcohol; sparingly soluble in propylene glycol; very slightly soluble in hexane; practically insoluble in water.

Smallpox Vaccine: Liquid Vaccine is a turbid, whitish to greenish suspension, which may have a slight odor due to the antimicrobial agent. Dried Vaccine is a yellow to grayish pellet, which may or may not become fragmented when shaken.

Soda Lime: White or grayish-white granules. May have a color if an indicator has been added. *NF category:* Sorbent, carbon dioxide.

Sodium Acetate: Colorless, transparent crystals, or white, granular crystalline powder, or white flakes. Is odorless or has a faint acetous odor, and has a slightly bitter, saline taste. Is efflorescent in warm, dry air. Very soluble in water; soluble in alcohol. *NF category:* Buffering agent.

Sodium Alginate: Practically odorless and tasteless, coarse or fine powder, yellowish white in color. Soluble in water, forming a viscous, colloidal solution; insoluble in alcohol and in hydroalcoholic solutions in which the alcohol content is greater than about 30% by weight, in chloroform, in ether, and in acids when the pH of the resulting solution becomes lower than about 3. *NF category:* Suspending and/or viscosity-increasing agent.

Sodium Ascorbate: White or very faintly yellow crystals or crystalline powder. Is odorless or practically odorless. Is relatively stable in air. On exposure to light it gradually darkens. Freely soluble in water; very slightly soluble in alcohol; insoluble in chloroform and in ether.

Sodium Benzoate: White, odorless or practically odorless, granular or crystalline powder. Is stable in air.

Freely soluble in water; soluble in 90% alcohol; sparingly soluble in alcohol. *NF category*: Antimicrobial preservative.

Sodium Bicarbonate: White, crystalline powder. Is stable in dry air, but slowly decomposes in moist air. Its solutions, when freshly prepared with cold water, without shaking, are alkaline to litmus. The alkalinity increases as the solutions stand, as they are agitated, or as they are heated. Soluble in water; insoluble in alcohol. *NF category*: Alkalizing agent.

Sodium Bisulfite: White, crystalline powder. Freely soluble in cold water and in hot water; sparingly soluble in alcohol. *NF category*: Antioxidant.

Sodium Borate: Colorless, transparent crystals or white, crystalline powder. Is odorless. Its solutions are alkaline to phenolphthalein TS. As it effloresces in warm, dry air, the crystals are often coated with white powder. Freely soluble in boiling water and in glycerin; soluble in water; insoluble in alcohol. *NF category*: Alkalizing agent.

Sodium Bromide: White, crystalline powder or colorless, cubical crystals. Freely soluble in water; soluble in alcohol.

Sodium Butyrate: Clear, colorless, hygroscopic powder. Soluble in water and in methanol. Melting range is about 250° to 253°.

Sodium Caprylate: A white, crystalline powder. Very soluble or freely soluble in water; freely soluble in acetic acid; sparingly soluble in alcohol; practically insoluble in acetone.

Sodium Carbonate: Colorless crystals, or white, crystalline powder or granules. Is stable in air under ordinary conditions. When exposed to dry air above 50°, the hydrous salt effloresces and, at 100°, becomes anhydrous. Very soluble in boiling water; freely soluble in water. *NF category*: Alkalizing agent.

Sodium Cetostearyl Sulfate: A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; slightly soluble in alcohol; practically insoluble in cold water.

Sodium Chloride: Colorless, cubic crystals or white crystalline powder. Has a saline taste. Freely soluble in water; soluble in glycerin; slightly soluble in alcohol. *NF category*: Tonicity agent.

Sodium Chloride Inhalation Solution: Clear, colorless solution.

Bacteriostatic Sodium Chloride Injection: Clear, colorless solution, odorless or having the odor of the bacteriostatic substance. *NF category*: Vehicle (sterile).

Sodium Chloride Irrigation: Clear, colorless solution.

Sodium Citrate: Colorless crystals, or white, crystalline powder. Hydrous form very soluble in boiling water; freely soluble in water; insoluble in alcohol. *NF category*: Buffering agent.

Sodium Citrate and Citric Acid Oral Solution: Clear solution having the color of any added preservative or flavoring agents.

Sodium Dehydroacetate: White or practically white, odorless powder, having a slight characteristic taste. Freely soluble in water, in propylene glycol, and in glycerin. *NF category*: Antimicrobial preservative.

Sodium Fluoride: White, odorless powder. Soluble in water; insoluble in alcohol.

Sodium Formaldehyde Sulfoxylate: White crystals or hard, white masses, having the characteristic odor of garlic. Freely soluble in water; slightly soluble in alcohol, in ether, in chloroform, and in benzene. *NF category*: Antioxidant.

Sodium Hydroxide: White, or practically white, fused masses, in small pellets, in flakes, or sticks, and in other forms. Is hard and brittle and shows a crystalline fracture. Exposed to the air, it rapidly absorbs carbon dioxide and moisture. Freely soluble in water and in alcohol. *NF category*: Alkalizing agent.

Sodium Hypochlorite Solution: Clear, pale greenish-yellow liquid, having the odor of chlorine. Is affected by light.

Sodium Iodide: Colorless, odorless crystals, or white, crystalline powder. Is deliquescent in moist air, and develops a brown tint upon decomposition. Very soluble in water; freely soluble in alcohol and in glycerin.

Sodium Lactate Solution: Clear, colorless or practically colorless, slightly viscous liquid, odorless or having a slight, not unpleasant odor. Miscible with water. *NF category*: Buffering agent.

Sodium Lauryl Sulfate: Small, white or light yellow crystals having a slight, characteristic odor. Freely soluble in water, forming an opalescent solution. *NF category*: Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sodium Metabisulfite: White crystals or white to yellowish, crystalline powder, having the odor of sulfur dioxide. Freely soluble in water and in glycerin; slightly soluble in alcohol. *NF category*: Antioxidant.

Sodium Monofluorophosphate: White to slightly gray, odorless powder. Freely soluble in water.

Sodium Nitrite: White to slightly yellow, granular powder, or white or practically white, opaque, fused masses or sticks. Has a mild, saline taste and is deliquescent in air. Its solutions are alkaline to litmus. Freely soluble in water; sparingly soluble in alcohol.

Sodium Nitrite Injection: Clear, colorless liquid.

Sodium Nitroprusside: Reddish-brown, practically odorless, crystals or powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; insoluble in benzene.

Dibasic Sodium Phosphate (dried): White powder that readily absorbs moisture. Freely soluble in water; insoluble in alcohol. *NF category*: Buffering agent.

Dibasic Sodium Phosphate (heptahydrate): Colorless or white, granular or caked salt. Effloresces in warm, dry air. Its solutions are alkaline to phenolphthalein TS, a 0.1 M solution having a pH of about 9. Freely soluble in water; very slightly soluble in alcohol. *NF category*: Buffering agent.

Monobasic Sodium Phosphate: Colorless crystals or white, crystalline powder. Is odorless and is slightly deliquescent. Its solutions are acid to litmus and effervesce with sodium carbonate. Freely soluble in water; practically insoluble in alcohol. *NF category*: Buffering agent.

Tribasic Sodium Phosphate: The formula for a crystalline material is approximately $4(\text{Na}_3\text{PO}_4 \cdot 12\text{H}_2\text{O})\text{NaOH}$. It occurs as white, odorless crystals or granules or as a crystalline powder. Freely soluble in water; insoluble in alcohol. The pH of a 1 in 100 solution is between 11.5 and 12.0.

Sodium Polystyrene Sulfonate: Golden brown, fine powder. Is odorless and has a characteristic taste. Insoluble in water.

Sodium Propionate: Colorless, transparent crystals or granular, crystalline powder. Is odorless, or has a faint acetic-butyric odor and is deliquescent in moist air. Very soluble in water; soluble in alcohol. *NF category*: Antimicrobial preservative.

Sodium Salicylate: Amorphous or microcrystalline powder or scales. Is colorless, or has not more than a faint, pink tinge. Is odorless, or has a faint, characteristic odor, and is affected by light. A freshly made solution (1 in 10) is neutral or acid to litmus. Very soluble in boiling water and in boiling alcohol; freely (and slowly) soluble in water and in glycerin; slowly soluble in alcohol.

Sodium Starch Glycolate: White, tasteless, odorless, relatively free-flowing powder; available in several different viscosity grades. A 2% (w/v) dispersion in cold water settles, on standing, in the form of a highly hydrated layer. *NF category*: Tablet disintegrant.

Sodium Stearate: Fine, white powder, soapy to the touch, usually having a slight, tallow-like odor. Is affected by light. Its solutions are alkaline to phenolphthalein TS. Slowly soluble in cold water and in cold alcohol; readily soluble in hot water and in hot alcohol. *NF category:* Emulsifying and/or solubilizing agent.

Sodium Stearyl Fumarate: Fine, white powder. Slightly soluble in methanol; practically insoluble in water. *NF category:* Tablet and/or capsule lubricant.

Sodium Sulfate: Large, colorless, odorless, transparent crystals, or a granular powder. Effloresces rapidly in air, liquefies in its water of hydration at about 33°, and loses all of its water of hydration at about 100°. Freely soluble in water; soluble in glycerin; insoluble in alcohol.

Sodium Sulfite: Colorless crystals. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Antioxidant.

Sodium Tartrate: Transparent, colorless, odorless crystals. Freely soluble in water; insoluble in alcohol. *NF category:* Sequestering agent.

Sodium Thiosulfate: Large, colorless crystals or coarse, crystalline powder. Is deliquescent in moist air and effloresces in dry air at temperatures exceeding 33°. Its solutions are neutral or faintly alkaline to litmus. Very soluble in water; insoluble in alcohol. *NF category:* Antioxidant.

Sorbic Acid: Free-flowing, white, crystalline powder, having a characteristic odor. Soluble in alcohol and in ether; slightly soluble in water. *NF category:* Antimicrobial preservative.

Sorbitan Monolaurate: Yellow to amber-colored, oily liquid, having a bland, characteristic odor. Soluble in mineral oil; slightly soluble in cottonseed oil and in ethyl acetate; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitan Monooleate: Viscous, yellow to amber-colored, oily liquid, having a bland, characteristic odor. Insoluble in water and in propylene glycol. Miscible with mineral and vegetable oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitan Monopalmitate: Cream-colored, waxy solid having a faint fatty odor. Soluble in warm absolute alcohol; soluble, with haze, in warm peanut oil and in warm mineral oil; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitan Monostearate: Cream-colored to tan, hard, waxy solid, having a bland odor and taste. Soluble, with haze, above 50° in mineral oil and in ethyl acetate; insoluble in cold water and in acetone. Dispersible in warm water. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitan Sesquileate: Viscous, yellow to amber-colored, oily liquid. Soluble in alcohol, in isopropyl alcohol, in cottonseed oil, and in mineral oil; insoluble in water and in propylene glycol. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitan Trioleate: Yellow to amber-colored, oily liquid. Soluble in methyl alcohol, in alcohol, in isopropyl alcohol, in corn oil, in cottonseed oil, and in mineral oil; insoluble in water, in ethylene glycol, and in propylene glycol. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitol: D-Sorbitol occurs as white granules, powder, or crystalline masses. Is odorless, and has a sweet taste with a cold sensation. Very soluble in water; sparingly soluble in alcohol; and practically insoluble in ethyl ether. Is hygroscopic. *NF category:* Humectant; sweetening agent; tablet and/or capsule diluent.

Sorbitol Solution: Clear, colorless, syrupy liquid. Is odorless and has a sweet taste. It sometimes separates into crystalline masses. Miscible with water, with alcohol, with glycerin, and with propylene glycol. Is neutral to litmus. *NF category:* Sweetening agent; vehicle (flavored and/or sweetened).

Sorbitol Sorbitan Solution: A clear, colorless to pale yellow, syrupy liquid. Is odorless and has a sweet taste. Insoluble in mineral oil and in vegetable oil. Miscible with water, with alcohol, with glycerin, and with propylene glycol. *NF category:* Humectant; plasticizer.

Sotalol Hydrochloride: White to off-white powder. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform.

Soybean Oil: Clear, pale yellow, oily liquid having a characteristic odor and taste. Insoluble in water. Miscible with ether and with chloroform. *Specific gravity* (841): between 0.916 and 0.922. *Refractive index* (831): between 1.465 and 1.475. *NF category:* Vehicle (oleaginous).

Hydrogenated Soybean Oil: A white mass or powder that melts to a clear, pale yellow liquid when heated. Freely soluble in methylene chloride, in hexane after heating, and in toluene; very slightly soluble in alcohol; practically insoluble in water. *NF category:* Emollient.

Spectinomycin Hydrochloride: White to pale-buff crystalline powder. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether.

Spironolactone: Light cream-colored to light tan, crystalline powder. Has a faint to mild mercaptan-like odor; is stable in air. Freely soluble in benzene and in chloroform; soluble in ethyl acetate and in alcohol; slightly soluble in methanol and in fixed oils; practically insoluble in water.

Squalane: Colorless, practically odorless transparent oil. Slightly soluble in acetone; very slightly soluble in absolute alcohol; insoluble in water. Miscible with ether and with chloroform. *NF category:* Ointment base; vehicle (oleaginous).

Stannous Chloride: White, crystalline powder or colorless crystals, efflorescent in air. Freely soluble in water (the solution becomes cloudy after standing or on dilution) and in alcohol. Dissolves in dilute hydrochloric acid. *NF category:* Emulsifying agent; antioxidant.

Stannous Fluoride: White, crystalline powder, having a bitter, salty taste. Melts at about 213°. Freely soluble in water; practically insoluble in alcohol, in ether, and in chloroform.

Stanozolol: Odorless, crystalline powder, occurring in two forms: as needles, melting at about 155°, and as prisms, melting at about 235°. Soluble in dimethylformamide; sparingly soluble in alcohol and in chloroform; slightly soluble in ethyl acetate and in acetone; very slightly soluble in benzene; insoluble in water.

Delete the following:

■**Starch:** Irregular, angular, white masses or fine powder. Is odorless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. *NF category:* Tablet and/or capsule diluent; tablet disintegrant; tablet and/or capsule lubricant. ■^{1S} (NF31)

Change to read:

Corn Starch: Irregular, angular, white masses ■(which may be bleached) ■^{1S} (NF31) or fine powder. Is odorless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. *NF category:* Tablet and/or capsule diluent; tablet disintegrant; tablet binder; suspending and/or viscosity-increasing agent.

Hydroxypropyl Corn Starch: White or slightly yellowish powder. Practically insoluble in cold water and in alcohol. *NF category:* Tablet binder; tablet and/or capsule diluent; tablet disintegrant; suspending and/or viscosity-increasing agent.

Pregelatinized Hydroxypropyl Corn Starch: White or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Pea Starch: White or almost white, very fine powder. Practically insoluble in cold water and in alcohol. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Hydroxypropyl Pea Starch: White or slightly yellowish powder. Practically insoluble in cold water and in alcohol. *NF category:* Tablet binder; tablet and/or capsule diluent; tablet disintegrant; suspending and/or viscosity-increasing agent.

Pregelatinized Hydroxypropyl Pea Starch: White or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Change to read:

Potato Starch: Irregular, angular, white masses ■(which may be bleached)■^{1S (NF31)} or fine powder. Is odorless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. *NF category:* Tablet and/or capsule diluent; tablet disintegrant; tablet binder; suspending and/or viscosity-increasing agent.

Hydroxypropyl Potato Starch: White or slightly yellowish powder. Practically insoluble in cold water and in alcohol. *NF category:* Tablet binder; tablet and/or capsule diluent; tablet disintegrant; suspending and/or viscosity-increasing agent.

Pregelatinized Hydroxypropyl Potato Starch: White or slightly yellowish powder. It swells in water and produces a clear or translucent, viscous, colloidal mixture. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Pregelatinized Starch: Moderately coarse to fine, white to off-white powder. Is odorless and has a slight, characteristic taste. Slightly soluble to soluble in cold water; insoluble in alcohol. *NF category:* Tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Pregelatinized Modified Starch: Moderately coarse to fine, white to off-white powder. Is odorless and has a slight, characteristic taste. Soluble to slightly soluble in cold water; insoluble in alcohol. *NF category:* Tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Change to read:

Tapioca Starch: Irregular, angular, white to pale yellow masses ■(which may be bleached)■^{1S (NF31)} or fine powder. Insoluble in cold water and in alcohol. *NF category:* Suspending and/or viscosity-increasing agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant.

Change to read:

Wheat Starch: Irregular, angular, white masses ■(which may be bleached)■^{1S (NF31)} or fine powder. Is odorless and has a slight, characteristic taste. Insoluble in cold water and in alcohol. *NF category:* Tablet and/or capsule diluent; tablet disintegrant; tablet binder; suspending and/or viscosity-increasing agent.

Hydrogenated Starch Hydrolysate: Concentrated, aqueous solution or spray-dried or dried powder. Very soluble in water; insoluble in alcohol. *NF category:* Sweetening agent; humectant; tablet binder; tablet and/or capsule diluent.

Stavudine: White to off-white, crystalline powder. Soluble in water, in dimethylacetamide, and in dimethyl sulfoxide; sparingly soluble in methanol, in alcohol, and in acetonitrile; slightly soluble in dichloromethane; insoluble in hexane.

Stearic Acid: Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or white or yellowish-white powder. Its odor and taste are slight, suggesting tallow. Freely soluble in chloroform and in ether; soluble in alcohol; practically insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant.

Purified Stearic Acid: Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or white or yellowish-white powder. Its odor and taste are slight, suggesting tallow. Freely soluble in chloroform and in ether; soluble in alcohol; practically insoluble in water. *NF category:* Tablet and/or capsule lubricant.

Stearyl Polyoxylglycerides: Pale yellow, waxy solids. Dispersible in warm water and in warm paraffin. Freely soluble in methylene chloride; soluble in warm methanol. *NF category:* Ointment base; solvent.

Stearyl Alcohol: Unctuous, white flakes or granules. Has a faint, characteristic odor and a bland, mild taste. Soluble in alcohol and in ether; insoluble in water. *NF category:* Stiffening agent.

Storax: Semiliquid, grayish to grayish-brown, sticky, opaque mass depositing on standing a heavy dark brown layer (Levant Storax); or semisolid, sometimes a solid mass, softened by gently warming (American Storax). Is transparent in thin layers, has a characteristic odor and taste, and is more dense than water. Soluble, usually incompletely, in an equal weight of warm alcohol, in acetone, in carbon disulfide, and in ether, some insoluble residue usually remaining; insoluble in water.

Streptomycin Sulfate: White or practically white powder. Is odorless or has not more than a faint odor. Is hygroscopic, but is stable in air and on exposure to light. Its solutions are acid to practically neutral to litmus. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform.

Streptomycin Sulfate Injection: Clear, colorless to yellow, viscous liquid. Is odorless or has a slight odor.

Strontium Chloride: Colorless, odorless crystals or white granules. Effloresces in air; deliquesces in moist air. Very soluble in water; soluble in alcohol.

Succinic Acid: White, odorless crystals. Freely soluble in boiling water; soluble in water, in alcohol, and in glycerin. *NF category:* Buffering agent.

Succinylcholine Chloride: White, odorless, crystalline powder. Its solutions have a pH of about 4. The dihydrate form melts at about 160°; the anhydrous form melts at about 190°, and is hygroscopic. Freely soluble in water; slightly soluble in alcohol and in chloroform; practically insoluble in ether.

Sucralose: White to off-white, crystalline powder. Freely soluble in water, in methanol, and in alcohol; slightly soluble in ethyl acetate. *NF category:* Sweetening agent.

Sucrose: White, crystalline powder or lustrous, dry, colorless or white crystals. Very soluble in water; slightly soluble in alcohol; practically insoluble in dehydrated alcohol. *NF category:* Coating agent; sweetening agent; tablet and/or capsule diluent.

Sucrose Palmitate: White or almost white, unctuous powder. Sparingly soluble in ethanol (96%); very slightly soluble in water. *NF category:* Suspending and/or viscosity-increasing agent.

Sucrose Octaacetate: White, practically odorless powder, having an intensely bitter taste. Is hygroscopic. Very soluble in methanol and in chloroform; soluble in alcohol and in ether; very slightly soluble in water. *NF category:* Alcohol denaturant.

Sucrose Stearate: White or almost white, unctuous powder. Sparingly soluble in ethanol (96%); very slightly soluble in water. *NF category:* Tablet and/or capsule lubricant; emulsifying and/or solubilizing agent.

Sufentanil Citrate: White powder. Freely soluble in methanol; soluble in water; sparingly soluble in acetone, in alcohol, and in chloroform. Melts between 133° and 140°.

Compressible Sugar: Practically white, crystalline, odorless powder, having a sweet taste. Is stable in air. The sucrose portion of Compressible Sugar is very soluble in water. *NF category:* Sweetening agent; tablet and/or capsule diluent.

Confectioner's Sugar: Fine, white, odorless powder, having a sweet taste. Is stable in air. The sucrose portion of Confectioner's Sugar is soluble in cold water. Confectioner's Sugar is freely soluble in boiling water. *NF category:* Sweetening agent; tablet and/or capsule diluent.

Sugar Spheres: Hard, brittle, free-flowing, spherical masses ranging generally in size from 10- to 60-mesh. Usually white, but may be colored. Solubility in water varies according to the sugar-to-starch ratio. *NF category:* Vehicle (solid carrier).

Sulbactam Sodium: White to off-white, crystalline powder. Freely soluble in water and in dilute acid; sparingly soluble in acetone, in ethyl acetate, and in chloroform.

Sulconazole Nitrate: White to off-white, crystalline powder. Melts at about 130°, with decomposition. Freely soluble in pyridine; sparingly soluble in methanol; slightly soluble in alcohol, in chloroform, in acetone, and in methylene chloride; very slightly soluble in water, in toluene, and in dioxane.

Sulfabenzamide: Fine, white, practically odorless powder. Soluble in alcohol, in acetone, and in sodium hydroxide TS; insoluble in water and in ether.

Sulfacetamide: White, crystalline powder, odorless and having a characteristic sour taste. Its aqueous solutions are sensitive to light, and are unstable when acidic or strongly alkaline. Freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides; soluble in alcohol; slightly soluble in water and in ether; very slightly soluble in chloroform; practically insoluble in benzene.

Sulfacetamide Sodium: White, crystalline powder. Is odorless and has a bitter taste. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether.

Sulfadiazine: White or slightly yellow powder. Is odorless or nearly odorless and is stable in air, but slowly darkens on exposure to light. Freely soluble in dilute mineral acids, in solutions of potassium and sodium hydroxides, and in ammonia TS; sparingly soluble in alcohol and in acetone; slightly soluble in human serum at 37°; practically insoluble in water.

Silver Sulfadiazine: White to creamy-white, crystalline powder, odorless to having a slight odor. Is stable in air, but turns yellow on exposure to light. Freely soluble in 30% ammonium solution; slightly soluble in acetone; practically insoluble in alcohol, in chloroform, and in ether. Decomposes in moderately strong mineral acids.

Sulfadiazine Sodium: White powder. On prolonged exposure to humid air it absorbs carbon dioxide with the liberation of sulfadiazine and becomes incompletely soluble in water. Its solutions are alkaline to phenolphthalein. Is affected by light. Freely soluble in water; slightly soluble in alcohol.

Sulfadimethoxine: Practically white, crystalline powder. Soluble in 2 N sodium hydroxide; sparingly soluble in 2 N

hydrochloric acid; slightly soluble in alcohol, in ether, in chloroform, and in hexane; practically insoluble in water.

Sulfamethazine: White to yellowish-white powder, which may darken on exposure to light. Has a slightly bitter taste and is practically odorless. Soluble in acetone; slightly soluble in alcohol; very slightly soluble in water and in ether.

Sulfamethizole: White crystals or powder, having a slightly bitter taste. Is practically odorless, and has no odor of hydrogen sulfide. Freely soluble in solutions of ammonium, potassium, and sodium hydroxides; soluble in dilute mineral acids and in acetone; sparingly soluble in alcohol; very slightly soluble in water, in chloroform, and in ether; practically insoluble in benzene.

Sulfamethoxazole: White to off-white, practically odorless, crystalline powder. Freely soluble in acetone and in dilute solutions of sodium hydroxide; sparingly soluble in alcohol; practically insoluble in water, in ether, and in chloroform.

Sulfapyridine: White or faintly yellowish-white crystals, granules, or powder. Is odorless or practically odorless, and is stable in air, but slowly darkens on exposure to light. Freely soluble in dilute mineral acids and in solutions of potassium and sodium hydroxides; sparingly soluble in acetone; slightly soluble in alcohol; very slightly soluble in water.

Sulfasalazine: Bright yellow or brownish-yellow, odorless, fine powder. Melts at about 255°, with decomposition. Soluble in aqueous solutions of alkali hydroxides; very slightly soluble in alcohol; practically insoluble in water, in ether, in chloroform, and in benzene.

Sulfathiazole: Fine, white or faintly yellowish-white, practically odorless powder. Soluble in acetone, in dilute mineral acids, in solutions of alkali hydroxides, and in 6 N ammonium hydroxide; slightly soluble in alcohol; very slightly soluble in water.

Sulfipyrazone: White to off-white powder. Soluble in alcohol and in acetone; sparingly soluble in dilute alkali; practically insoluble in water and in solvent hexane.

Sulfisoxazole: White to slightly yellowish, odorless, crystalline powder. Soluble in boiling alcohol and in 3 N hydrochloric acid; very slightly soluble in water.

Sulfisoxazole Acetyl: White or slightly yellow, crystalline powder. Sparingly soluble in chloroform; slightly soluble in alcohol; practically insoluble in water.

Precipitated Sulfur: Very fine, pale yellow, amorphous or microcrystalline powder. Is odorless and tasteless. Very soluble in carbon disulfide; slightly soluble in olive oil; very slightly soluble in alcohol; practically insoluble in water.

Sublimed Sulfur: Fine, yellow, crystalline powder, having a faint odor and taste. Sparingly soluble in olive oil; practically insoluble in water and in alcohol.

Sulfur Dioxide: Colorless, nonflammable gas, possessing a strong, suffocating odor characteristic of burning sulfur. Under pressure, it condenses readily to a colorless liquid that boils at –10° and has a density of approximately 1.5. At 20° and at standard pressure, approximately 36 volumes dissolve in 1 volume of water and approximately 114 volumes dissolve in 1 volume of alcohol. Soluble also in ether and in chloroform. *NF category:* Antioxidant.

Sulfuric Acid: Clear, colorless, oily liquid. Miscible with water and with alcohol with the generation of much heat. Is very caustic and corrosive. Specific gravity is about 1.84. *NF category:* Acidifying agent.

Sulindac: Yellow, crystalline powder, which is odorless or practically so. Slightly soluble in methanol, in alcohol, in acetone, and in chloroform; very slightly soluble in isopropanol and in ethyl acetate; practically insoluble in hexane and in water.

Sulisobenzone: Light tan powder, with a melting point of about 145°. Freely soluble in methanol, in alcohol, and in water; sparingly soluble in ethyl acetate.

Sumatriptan: White to pale yellow powder. Very slightly soluble in water.

Sumatriptan Succinate: White or almost white powder. Freely soluble in water; sparingly soluble in methanol; practically insoluble in methylene chloride.

Suprofen: White to off-white powder, odorless to having a slight odor. Sparingly soluble in water.

Syrup: *NF category:* Sweetening agent; tablet binder; vehicle (flavored and/or sweetened).

Tacrine Hydrochloride: White powder. Freely soluble in water, in 0.1 N hydrochloric acid, in pH 4.0 acetate buffer, in phosphate buffer (pH between 7.0 and 7.4), in methanol, in dimethylsulfoxide, in alcohol, and in propylene glycol; sparingly soluble in linoleic acid and in polyethylene glycol 400.

Add the following:

■**Tacrolimus:** White crystals or white crystalline powder. Very soluble in methanol; freely soluble in *N,N*-dimethylformamide, and in alcohol; practically insoluble in water. ■*US (USP36)*

Add the following:

▲**Tadalafil:** White or almost white powder. Freely soluble in dimethyl sulfoxide; slightly soluble in methylene chloride; practically insoluble in water. ▲*USP36*

Tagatose: White or almost white crystals, having a sweet taste. Very soluble in water; very slightly soluble in alcohol. *NF category:* Sweetening agent; humectant.

Talc: Very fine, white or grayish-white, crystalline powder. Is unctuous, adheres readily to the skin, and is free from grittiness. *NF category:* Glidant and/or anticaking agent; tablet and/or capsule lubricant.

Tamoxifen Citrate: White, fine, crystalline powder. Soluble in methanol; very slightly soluble in water, in acetone, in chloroform, and in alcohol. Melts at about 142°, with decomposition.

Tamsulosin Hydrochloride: White or almost white crystalline powder. Melts with decomposition at approximately 230°. Freely soluble in formic acid; sparingly soluble in methanol; slightly soluble in water and in dehydrated alcohol; practically insoluble in ether.

Tannic Acid: Amorphous powder, glistening scales, or spongy masses, varying in color from yellowish-white to light brown. Is odorless or has a faint, characteristic odor, and has a strongly astringent taste. Very soluble in water, in acetone, and in alcohol; freely soluble in diluted alcohol; slightly soluble in dehydrated alcohol; practically insoluble in benzene, in chloroform, in ether, and in solvent hexane; 1 g dissolves in about 1 mL of warm glycerin.

Tartaric Acid: Colorless or translucent crystals or white, fine to granular, crystalline powder. Is odorless, has an acid taste, and is stable in air. Very soluble in water; freely soluble in alcohol. *NF category:* Acidifying agent.

Taurine: White crystals or crystalline powder. Soluble in water.

Tazobactam: White to pale yellow, nonhygroscopic, crystalline powder. Soluble in dimethylformamide; slightly soluble in water, in methanol, in acetone, and in alcohol; very slightly soluble in ethyl acetate, in ethyl ether, and in chloroform; insoluble in hexane.

Technetium Tc 99m Aggregated Albumin Injection: Milky suspension, from which particles settle upon standing.

Technetium Tc 99m Pentetate Injection: Clear, colorless solution.

Sodium Pertechnetate Tc 99m Injection: Clear, colorless solution.

Technetium Tc 99m (Pyro- and trimeta-) Phosphates Injection: Clear solution.

Technetium Tc 99m Sulfur Colloid Injection: Colloidal dispersion. Slightly opalescent, colorless to light tan liquid.

Telmisartan: White or slightly yellowish, crystalline powder. Sparingly soluble in methylene chloride; slightly soluble in methanol; practically insoluble in water. It dissolves in 1 M sodium hydroxide.

Temazepam: White or nearly white, crystalline powder. Sparingly soluble in alcohol; very slightly soluble in water. Melts between 157° and 163°, within a 3° range.

Temozolomide: White to light pink/light tan powder. Soluble in dimethyl sulfoxide; sparingly soluble in water; practically insoluble in toluene.

Terazosin Hydrochloride: White to pale yellow, crystalline powder. Freely soluble in isotonic saline solution; soluble in methanol and in water; slightly soluble in alcohol and in 0.1 N hydrochloric acid; very slightly soluble in chloroform; practically insoluble in acetone and in hexanes.

Terbinafine Hydrochloride: White or off-white powder. Freely soluble in dehydrated alcohol and in methanol; slightly soluble in acetone; very slightly or slightly soluble in water.

Terbutaline Sulfate: White to gray-white, crystalline powder. Is odorless or has a faint odor of acetic acid. Soluble in water and in 0.1 N hydrochloric acid; slightly soluble in methanol; insoluble in chloroform.

Terconazole: White to off-white powder. Freely soluble in methylene chloride; soluble in acetone; sparingly soluble in alcohol; practically insoluble in water. It exhibits polymorphism.

Terpin Hydrate: Colorless, lustrous crystals or white powder. Has a slight odor, and effloresces in dry air. A hot solution (1 in 100) is neutral to litmus. When dried in vacuum at 60° for 2 hours, it melts at about 103°. Very soluble in boiling alcohol; soluble in alcohol; sparingly soluble in boiling water; slightly soluble in water, in chloroform, and in ether.

Testolactone: White to off-white, practically odorless, crystalline powder. Melts at about 218°. Soluble in alcohol and in chloroform; slightly soluble in water and in benzyl alcohol; insoluble in ether and in solvent hexane.

Testosterone: White or slightly creamy white crystals or crystalline powder. Is odorless, and is stable in air. Freely soluble in dehydrated alcohol and in chloroform; soluble in dioxane and in vegetable oils; slightly soluble in ether; practically insoluble in water.

Testosterone Cypionate: White or creamy white, crystalline powder. Is odorless or has a slight odor, and is stable in air. Freely soluble in alcohol, in chloroform, in dioxane, and in ether; soluble in vegetable oils; insoluble in water.

Testosterone Enanthate: White or creamy white, crystalline powder. Is odorless or has a faint odor characteristic of heptanoic acid. Very soluble in ether; soluble in vegetable oils; insoluble in water.

Testosterone Propionate: White or creamy white crystals or crystalline powder. Is odorless and is stable in air. Freely soluble in alcohol, in dioxane, in ether, and in other organic solvents; soluble in vegetable oils; insoluble in water.

Tetanus Immune Globulin: Transparent or slightly opalescent liquid, practically colorless and practically odorless. May develop a slight granular deposit during storage.

Tetanus Toxoid: Clear, colorless to brownish-yellow, or slightly turbid liquid, free from evident clumps or particles, having a characteristic odor or an odor of formaldehyde.

Tetanus Toxoid Adsorbed: Turbid, white, slightly gray, or slightly pink suspension, free from evident clumps after shaking.

Tetanus and Diphtheria Toxoids Adsorbed for Adult Use: Turbid, white, slightly gray, or cream-colored suspension, free from evident clumps after shaking.

Tetracaine: White or light yellow, waxy solid. Soluble in alcohol, in ether, in benzene, and in chloroform; very slightly soluble in water.

Tetracaine Hydrochloride: Fine, white, crystalline, odorless powder. Has a slightly bitter taste followed by a sense of numbness. Its solutions are neutral to litmus. Melts at about 148°, or may occur in either of two other polymorphic modifications that melt at about 134° and 139°, respectively. Mixtures of the forms may melt within the range of 134° to 147°. Is hygroscopic. Very soluble in water; soluble in alcohol; insoluble in ether and in benzene.

Tetracycline: Yellow, odorless, crystalline powder. Is stable in air, but exposure to strong sunlight causes it to darken. It loses potency in solutions of pH below 2, and is rapidly destroyed by alkali hydroxide solutions. Freely soluble in dilute acid and in alkali hydroxide solutions; sparingly soluble in alcohol; very slightly soluble in water; practically insoluble in chloroform and in ether.

Tetracycline Hydrochloride: Yellow, odorless, crystalline powder. Is moderately hygroscopic. Is stable in air, but exposure to strong sunlight in moist air causes it to darken. It loses potency in solution at a pH below 2, and is rapidly destroyed by alkali hydroxide solutions. Soluble in water and in solutions of alkali hydroxides and carbonates; slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Tetrahydrozoline Hydrochloride: White, odorless solid. Melts at about 256°, with decomposition. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether.

Thalidomide: White to off-white powder. Very soluble in dimethylformamide, in dioxane, and in pyridine; sparingly soluble in acetone, in butyl acetate, in ethanol, in ethyl acetate, in glacial acetic acid, in methanol, and in water; practically insoluble in benzene, in chloroform, and in ether.

Theophylline: White, odorless, crystalline powder, having a bitter taste. Is stable in air. Freely soluble in solutions of alkali hydroxides and in ammonia; sparingly soluble in alcohol, in chloroform, and in ether; slightly soluble in water, but more soluble in hot water.

Theophylline Sodium Glycinate: White, crystalline powder having a slight ammoniacal odor and a bitter taste. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform.

Thiabendazole: White to practically white, odorless or practically odorless powder. Slightly soluble in acetone and in alcohol; very slightly soluble in chloroform and in ether; practically insoluble in water.

Thiacetarsamide: White to yellowish, crystalline powder. Soluble in warm dehydrated alcohol and in warm methanol; sparingly soluble in cold dehydrated alcohol, in cold methanol, and in cold water; more soluble in water above 90°; insoluble in warm isopropyl alcohol. pK_a is 4.

Thiamine Hydrochloride: White crystals or crystalline powder, usually having a slight, characteristic odor. When exposed to air, the anhydrous product rapidly absorbs about 4% of water. Melts at about 248°, with some decomposition. Freely soluble in water; soluble in glycerin; slightly soluble in alcohol; insoluble in ether and in benzene.

Thiamine Mononitrate: White crystals or crystalline powder, usually having a slight, characteristic odor. Sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform.

Thiethylperazine Maleate: Yellowish, granular powder. Is odorless or has not more than a slight odor. Melts at

about 183°, with decomposition. Slightly soluble in methanol; practically insoluble in water and in chloroform.

Thimerosal: Light cream-colored, crystalline powder, having a slight characteristic odor. Is affected by light. The pH of a solution (1 in 100) is about 6.7. Freely soluble in water; soluble in alcohol; practically insoluble in ether. *NF* category: Antimicrobial preservative.

Thimerosal Topical Solution: Clear liquid, having a slight characteristic odor. Is affected by light.

Thimerosal Tincture: Transparent, mobile liquid, having the characteristic odor of alcohol and acetone. Is affected by light.

Thioguanine: Pale yellow, odorless or practically odorless, crystalline powder. Freely soluble in dilute solutions of alkali hydroxides; insoluble in water, in alcohol, and in chloroform.

Thiopental Sodium: White to off-white, crystalline powder, or yellowish-white to pale greenish-yellow, hygroscopic powder. May have a disagreeable odor. Its solutions are alkaline to litmus. Its solutions decompose on standing, and on boiling precipitation occurs. Soluble in water and in alcohol; insoluble in benzene, in absolute ether, and in solvent hexane.

Thiopental Sodium for Injection: White to off-white, crystalline powder, or yellowish-white to pale greenish-yellow, hygroscopic powder. May have a disagreeable odor. Its solutions are alkaline to litmus. Its solutions decompose on standing, and on boiling precipitation occurs.

Thioridazine: White to slightly yellow, crystalline or micronized powder, odorless or having a faint odor. Very soluble in chloroform; freely soluble in dehydrated alcohol and in ether; practically insoluble in water.

Thioridazine Hydrochloride: White to slightly yellow, granular powder, having a faint odor and a very bitter taste. Freely soluble in water, in methanol, and in chloroform; insoluble in ether.

Thiostrepton: White to off-white, crystalline solid. Soluble in glacial acetic acid, in chloroform, in dimethylformamide, in dimethyl sulfoxide, in dioxane, and in pyridine; practically insoluble in water, in the lower alcohols, in nonpolar organic solvents, and in dilute aqueous acids or alkali.

Thiotepa: Fine, white, crystalline flakes, having a faint odor. Freely soluble in water, in alcohol, in chloroform, and in ether.

Thiotepa for Injection: White powder.

Thiothixene: White to tan, practically odorless crystals. Is affected by light. Very soluble in chloroform; slightly soluble in methanol and in acetone; practically insoluble in water.

Thiothixene Hydrochloride: White, or practically white, crystalline powder, having a slight odor. Is affected by light. Soluble in water; slightly soluble in chloroform; practically insoluble in benzene, in acetone, and in ether.

Threonine: White, odorless crystals, having a slightly sweet taste. Freely soluble in water; insoluble in absolute alcohol, in ether, and in chloroform.

Thrombin: White to grayish, amorphous substance dried from the frozen state.

Thymol: Colorless, often large, crystals, or white, crystalline powder, having an aromatic, thyme-like odor and a pungent taste. Is affected by light. Its alcohol solution is neutral to litmus. Freely soluble in alcohol, in chloroform, in ether, and in olive oil; soluble in glacial acetic acid and in fixed and volatile oils; very slightly soluble in water. *NF* category: Antimicrobial preservative; flavors and perfumes.

Thyroid: Yellowish to buff-colored, amorphous powder, having a slight, characteristic, meat-like odor and a saline taste.

Tiagabine Hydrochloride: White to off-white powder. Freely soluble in methanol and in alcohol; soluble in isopro-

panol; very slightly soluble in chloroform; sparingly soluble in water; practically insoluble in *n*-heptane.

Tiamulin: A sticky, translucent yellowish mass, slightly hygroscopic. Very soluble in dichloromethane; freely soluble in dehydrated alcohol; practically insoluble in water.

Ticarcillin Disodium: White to pale yellow powder, or white to pale yellow solid. Freely soluble in water.

Ticlopidine: White or almost white crystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in ethyl acetate.

Tiletamine Hydrochloride: White to off-white, crystalline powder. Freely soluble in water and in 0.1 N hydrochloric acid; soluble in methanol; slightly soluble in chloroform; practically insoluble in ether.

Tilmicosin: White to off-white, amorphous solid. Slightly soluble in water and in *n*-hexane.

Timolol Maleate: White to practically white, odorless or practically odorless powder. Soluble in water, in alcohol, and in methanol; sparingly soluble in chloroform and in propylene glycol; insoluble in ether and in cyclohexane.

Tinidazole: Almost white or pale yellow, crystalline powder. Soluble in acetone and in methylene chloride; sparingly soluble in methanol; practically insoluble in water.

Titanium Dioxide: White, odorless, tasteless powder. Its 1 in 10 suspension in water is neutral to litmus. Insoluble in water, in hydrochloric acid, in nitric acid, and in 2 N sulfuric acid. Dissolves in hydrofluoric acid and in hot sulfuric acid. Is rendered soluble by fusion with potassium bisulfate or with alkali carbonates or hydroxides. *NF category:* Coating agent.

Tizanidine Hydrochloride: Almost white to slightly yellow, crystalline powder. Slightly soluble in water and in methanol.

Tobramycin: White to off-white, hygroscopic powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in chloroform and in ether.

Tobramycin Sulfate Injection: Clear, colorless solution.

Tocainide Hydrochloride: Fine, white, odorless powder. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Tocopherol: Clear, colorless to yellow, yellowish-brown, or greenish-yellow, viscous oil. Is odorless. Soluble in oils, in fats, in acetone, in alcohol, in chloroform, in ether, and in alcohol; insoluble in water. *NF category:* Antioxidant.

Tocopherols Excipient: Brownish-red to red, clear, viscous oil, having a mild, characteristic odor and taste. May show a slight separation of waxlike constituents in microcrystalline form. Oxidizes and darkens slowly in air and on exposure to light, particularly in alkaline media. Soluble in alcohol; insoluble in water. Miscible with acetone, with chloroform, with ether, and with vegetable oils. *NF category:* Antioxidant.

Tolazamide: White to off-white, crystalline powder, odorless or having a slight odor. Melts with decomposition in the approximate range of 161° to 173°. Freely soluble in chloroform; soluble in acetone; slightly soluble in alcohol; very slightly soluble in water.

Tolazoline Hydrochloride: White to off-white, crystalline powder. Its solutions are slightly acid to litmus. Freely soluble in water and in alcohol.

Tolbutamide: White, or practically white, crystalline powder. Is slightly bitter and practically odorless. Soluble in alcohol and in chloroform; practically insoluble in water.

Tolbutamide Sodium: White to off-white, practically odorless, crystalline powder, having a slightly bitter taste. Freely soluble in water; soluble in alcohol and in chloroform; very slightly soluble in ether.

Tolcapone: Yellow, fine powder or fine powder with lumps. Freely soluble in acetone and in tetrahydrofuran; soluble in methanol and in ethyl acetate; sparingly soluble in

chloroform and in dichloromethane; insoluble in water and in *n*-hexane.

Tolmetin Sodium: Light yellow to light orange, crystalline powder. Freely soluble in water and in methanol; slightly soluble in alcohol; very slightly soluble in chloroform.

Tolnaftate: White to creamy white, fine powder, having a slight odor. Freely soluble in acetone and in chloroform; sparingly soluble in ether; slightly soluble in alcohol; practically insoluble in water.

Tolu Balsam: Brown or yellowish-brown, plastic solid, transparent in thin layers and brittle when old, dried, or exposed to cold temperatures. Has a pleasant, aromatic odor resembling that of vanilla, and a mild, aromatic taste. Soluble in alcohol, in chloroform, and in ether, sometimes with slight residue or turbidity; practically insoluble in water and in solvent hexane. *NF category:* Flavors and perfumes.

Topiramate: White to off-white powder. Freely soluble in dichloromethane.

Torseimide: White to off-white, crystalline powder. Slightly soluble in 0.1 N sodium hydroxide, in 0.1 N hydrochloric acid, in alcohol, and in methanol; very slightly soluble in acetone and in chloroform; practically insoluble in water and in ether.

Tragacanth: Is odorless, and has an insipid, mucilaginous taste. *NF category:* Suspending and/or viscosity-increasing agent.

Tramadol Hydrochloride: White, crystalline powder. Freely soluble in water and in methanol; very slightly soluble in acetone.

Trandalopril: White or almost white powder. Freely soluble in methylene chloride; sparingly soluble in absolute alcohol; practically insoluble in water.

Tranexamic Acid: White, crystalline powder. Freely soluble in water and in glacial acetic acid; practically insoluble in acetone and in alcohol.

Tranlycypromine Sulfate: White or almost white crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in ether; practically insoluble in chloroform.

Travoprost: Clear, colorless, viscous oil. Insoluble in water.

Trazodone Hydrochloride: White to off-white, crystalline powder. Sparingly soluble in chloroform and in water. Melts between 231° and 234° when the melting point determination is carried out in an evacuated capillary tube; otherwise melts with decomposition over a broad range below 230°.

Trehalose: White, odorless, nonhygroscopic crystalline powder. Soluble in water, solubility increases with temperature; practically insoluble in dehydrated alcohol. Trehalose is typically used in the dihydrate form. *NF category:* Bulking agent for freeze drying; sweetening agent; tablet binder; tablet and/or capsule diluent; tablet disintegrant; vehicle (flavored and/or sweetened).

Tretinoin: Yellow to light-orange, crystalline powder. Slightly soluble in alcohol, in chloroform, and in methanol; insoluble in water.

Triacetin: Colorless, somewhat oily liquid having a slight, fatty odor and a bitter taste. Soluble in water; slightly soluble in carbon disulfide. Miscible with alcohol, with ether, and with chloroform. *NF category:* Plasticizer.

Triamcinolone: White or practically white, odorless, crystalline powder. Slightly soluble in alcohol and in methanol; very slightly soluble in water, in chloroform, and in ether.

Triamcinolone Acetonide: White to cream-colored, crystalline powder, having not more than a slight odor. Sparingly soluble in dehydrated alcohol, in chloroform, and in methanol; practically insoluble in water.

Triamcinolone Diacetate: Fine, white to off-white, crystalline powder, having not more than a slight odor. Soluble

in chloroform; sparingly soluble in alcohol and in methanol; slightly soluble in ether; practically insoluble in water.

Triamcinolone Hexacetonide: White to cream-colored powder. Soluble in chloroform; slightly soluble in methanol; practically insoluble in water.

Triamterene: Yellow, odorless, crystalline powder. Soluble in formic acid; sparingly soluble in methoxyethanol; very slightly soluble in acetic acid, in alcohol, and in dilute mineral acids; practically insoluble in water, in benzene, in chloroform, in ether, and in dilute alkali hydroxides.

Triazolam: White to off-white, practically odorless, crystalline powder. Soluble in chloroform; slightly soluble in alcohol; practically insoluble in ether and in water.

Tributyl Citrate: Clear, practically colorless, oily liquid. Freely soluble in alcohol, in isopropyl alcohol, in acetone, and in toluene; insoluble in water. *NF category:* Plasticizer.

Trichlorfon: White crystalline powder. Very soluble in methylene chloride; freely soluble in acetone, in alcohol, in benzene, in chloroform, in ether, and in water; very slightly soluble in hexane and in pentane. Decomposed by alkali. Melts at about 78° with decomposition.

Trichlormethiazide: White or practically white, crystalline powder. Is odorless, or has a slight characteristic odor. Melts at about 274°, with decomposition. Freely soluble in acetone; soluble in methanol; sparingly soluble in alcohol; very slightly soluble in water, in ether, and in chloroform.

Trichloromonofluoromethane: Clear, colorless gas, having a faint, ethereal odor. Its vapor pressure at 25° is about 796 mm of mercury (1 psig). *NF category:* Aerosol propellant.

Triclosan: Fine, whitish, crystalline powder. Melts at about 57°. Soluble in methanol, in alcohol, and in acetone; slightly soluble in hexane; practically insoluble in water.

Trientine Hydrochloride: White to pale yellow, crystalline powder. Melts at about 117°. Freely soluble in water; soluble in methanol; slightly soluble in alcohol; insoluble in chloroform and in ether.

Triethyl Citrate: Practically colorless, oily liquid. Soluble in water. Miscible with alcohol and with ether. *NF category:* Plasticizer.

Trifluoperazine Hydrochloride: White to pale yellow, crystalline powder. Is practically odorless, and has a bitter taste. Melts at about 242°, with decomposition. Freely soluble in water; soluble in alcohol; sparingly soluble in chloroform; insoluble in ether and in benzene.

Triflupromazine: Viscous, light amber-colored, oily liquid, which crystallizes on prolonged standing into large, irregular crystals. Practically insoluble in water.

Triflupromazine Hydrochloride: White to pale tan, crystalline powder, having a slight, characteristic odor. Melts between 170° and 178°. Soluble in water, in alcohol, and in acetone; insoluble in ether.

Trifluridine: Odorless, white powder appearing under the microscope as rodlike crystals; melts at 175°, with sublimation.

Medium-Chain Triglycerides: Colorless or slightly yellowish, oily liquid. Practically insoluble in water. Miscible with alcohol, with methylene chloride, with hexane, and with fatty oils.

Trihexyphenidyl Hydrochloride: White or slightly off-white, crystalline powder, having not more than a very faint odor. Melts at about 250°. Soluble in alcohol and in chloroform; slightly soluble in water.

Trimeprazine Tartrate: White to off-white, odorless, crystalline powder. Freely soluble in water and in chloroform; soluble in alcohol; very slightly soluble in ether and in benzene.

Trimethobenzamide Hydrochloride: White, crystalline powder having a slight phenolic odor. Soluble in water and in warm alcohol; insoluble in ether and in benzene.

Trimethoprim: White to cream-colored, odorless crystals, or crystalline powder. Soluble in benzyl alcohol; sparingly soluble in chloroform and in methanol; slightly soluble in alcohol and in acetone; very slightly soluble in water; practically insoluble in ether and in carbon tetrachloride.

Trimethoprim Sulfate: White to off-white, crystalline powder. Soluble in water, in alcohol, in dilute mineral acids, and in fixed alkalies.

Trimipramine Maleate: White to almost white crystalline powder. Slightly soluble in water and in alcohol.

Trioxsalen: White to off-white or grayish, odorless, crystalline solid. Melts at about 230°. Sparingly soluble in chloroform; slightly soluble in alcohol; practically insoluble in water.

Tripeleennamine Hydrochloride: White, crystalline powder. Slowly darkens on exposure to light. Its solutions are practically neutral to litmus. Freely soluble in water, in alcohol, and in chloroform; slightly soluble in acetone; insoluble in benzene, in ether, and in ethyl acetate.

Tripolidine Hydrochloride: White, crystalline powder, having no more than a slight, but unpleasant, odor. Its solutions are alkaline to litmus, and it melts at about 115°. Soluble in water, in alcohol, and in chloroform; insoluble in ether.

Trolamine: Colorless to pale yellow, viscous, hygroscopic liquid having a slight, ammoniacal odor. Soluble in chloroform. Miscible with water and with alcohol. *NF category:* Alkalizing agent; emulsifying and/or solubilizing agent.

Troleandomycin: White, odorless, crystalline powder. Freely soluble in alcohol; soluble in chloroform; slightly soluble in ether and in water.

Tromethamine: White, crystalline powder, having a slight, characteristic odor. Freely soluble in water.

Tropicamide: White or practically white, crystalline powder, odorless or having not more than a slight odor. Freely soluble in chloroform and in solutions of strong acids; slightly soluble in water.

Tropium Chloride: Colorless or white to slightly yellow crystalline powder. Very soluble in water; freely soluble in methanol.

Crystallized Trypsin: White to yellowish white, odorless, crystalline or amorphous powder.

Tryptophan: White to slightly yellowish-white crystals or crystalline powder, having a slightly bitter taste. Soluble in hot alcohol and in dilute hydrochloric acid.

Tuberculin: Old Tuberculin is a clear, brownish liquid, which is readily miscible with water and has a characteristic odor. Purified Protein Derivative (PPD) of Tuberculin is a very slightly opalescent, colorless solution. Old Tuberculin and PPD concentrates contain 50% of glycerin for use with various application devices. Old Tuberculin and PPD are also dried on the tines of multiple-puncture devices.

Tubocurarine Chloride: White or yellowish-white to grayish-white, crystalline powder. Melts at about 270°, with decomposition. Soluble in water; sparingly soluble in alcohol.

Tylosin: White to buff-colored powder. Freely soluble in methanol; soluble in alcohol, in amyl acetate, in chloroform, and in dilute mineral acids; slightly soluble in water.

Tylosin Tartrate: Almost white or slightly yellow, hygroscopic powder. Freely soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of mineral acids.

Tyloxapol: Viscous, amber liquid, having a slight, aromatic odor. May exhibit a slight turbidity. Slowly but freely miscible with water. Soluble in glacial acetic acid, in benzene, in toluene, in carbon tetrachloride, in chloroform, and in carbon disulfide. *NF category:* Wetting and/or solubilizing agent.

Tyrosine: White, odorless, tasteless crystals or crystalline powder. Very slightly soluble in water; insoluble in alcohol and in ether.

Ubidecarenone: Yellow to orange, crystalline powder. Melts at about 48°. Soluble in ether; very slightly soluble in dehydrated alcohol; practically insoluble in water.

Undecylenic Acid: Clear, colorless to pale yellow liquid having a characteristic odor. Practically insoluble in water. Miscible with alcohol, with chloroform, with ether, with benzene, and with fixed and volatile oils.

Urea: Colorless to white, prismatic crystals, or white, crystalline powder, or small white pellets. Is practically odorless, but may gradually develop a slight odor of ammonia upon long standing. Its solutions are neutral to litmus. Freely soluble in water and in boiling alcohol; practically insoluble in chloroform and in ether.

Urea C 13: See *Urea*.

Ursodiol: White or almost white, crystalline powder. Freely soluble in alcohol and in glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether; practically insoluble in water.

Vaccinia Immune Globulin: Transparent or slightly opalescent liquid. Is practically colorless and practically odorless. May develop a slight, granular deposit during storage.

Valacyclovir Hydrochloride: White to off-white powder. Soluble in water; insoluble in dichloromethane.

Powdered Valerian Extract: Brown, hygroscopic, powdery or easily pulverizable mass. Soluble in water to form a slightly cloudy solution; sparingly soluble in 70 percent alcohol; practically insoluble in alcohol.

Valganciclovir Hydrochloride: White to off-white powder. Very slightly soluble in alcohol; practically insoluble in 2-propanol, in hexane, in acetone, and in ethyl acetate.

Valine: White, odorless, tasteless crystals. Soluble in water; practically insoluble in ether, in alcohol, and in acetone.

Valproic Acid: Colorless to pale yellow, slightly viscous, clear liquid, having a characteristic odor. Refractive index: about 1.423 at 20°. Freely soluble in 1 N sodium hydroxide, in methanol, in alcohol, in acetone, in chloroform, in benzene, in ether, and in *n*-heptane; slightly soluble in water and in 0.1 N hydrochloric acid.

Valrubicin: Orange to orange-red, crystalline powder. Soluble in methylene chloride, in dehydrated alcohol, in methanol, and in acetone; very slightly soluble in water, in hexane, and in petroleum ether.

Valsartan: White or almost white, hygroscopic powder. Freely soluble in anhydrous ethanol; sparingly soluble in methylene chloride; practically insoluble in water.

Vancomycin Hydrochloride: White, almost white, or tan to brown, free-flowing powder, odorless, and having a bitter taste. Freely soluble in water; insoluble in ether and in chloroform.

Vanillin: Fine, white to slightly yellow crystals, usually needle-like, having an odor and taste suggestive of vanilla. Is affected by light. Its solutions are acid to litmus. Freely soluble in alcohol, in chloroform, in ether, and in solutions of the fixed alkali hydroxides; soluble in glycerin and in hot water; slightly soluble in water. *NF category:* Flavors and perfumes.

Vasopressin Injection: Clear, colorless or practically colorless liquid, having a faint, characteristic odor.

Vecuronium Bromide: White or creamy white crystals, or a crystalline powder. Sparingly soluble in alcohol; slightly soluble in water and in acetone.

Hydrogenated Vegetable Oil: Type I Hydrogenated Vegetable Oil—Fine, white powder, beads, or small flakes. Type II Hydrogenated Vegetable Oil—Plastic (semi-solid) or flakes having a softer consistency than Type I. Soluble in hot

isopropyl alcohol, in hexane, and in chloroform; insoluble in water. *NF category:* Type I Hydrogenated Vegetable Oil—Tablet and/or capsule lubricant; Type II Hydrogenated Vegetable Oil—Ointment base.

Venlafaxine Hydrochloride: Off-white to white crystalline powder. Soluble in methanol and in water.

Verapamil Hydrochloride: White or practically white, crystalline powder. Is practically odorless and has a bitter taste. Freely soluble in chloroform; soluble in water; sparingly soluble in alcohol; practically insoluble in ether.

Vidarabine: White to off-white powder. Slightly soluble in dimethylformamide; very slightly soluble in water.

Add the following:

■**Vigabatrin:** White or almost white powder. Freely soluble in water; slightly soluble in methanol; very slightly soluble in alcohol and in chloroform; practically insoluble in methylene chloride; insoluble in hexane and in toluene. ■ *USP 36*

Vinblastine Sulfate: White or slightly yellow, odorless, amorphous or crystalline powder. Is hygroscopic. Freely soluble in water.

Vincristine Sulfate: White to slightly yellow, odorless, amorphous or crystalline powder. Is hygroscopic. Freely soluble in water; soluble in methanol; slightly soluble in alcohol.

Vincristine Sulfate for Injection: Yellowish-white solid, having the characteristic appearance of products prepared by freeze-drying.

Vinorelbine Tartrate: White to yellow or light brown, amorphous powder. Freely soluble in water.

Vitamin A: In liquid form, a light-yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. May be practically odorless or may have a mild fishy odor, but has no rancid odor or taste. Is unstable to air and light. In liquid form, very soluble in chloroform and in ether; soluble in absolute alcohol and in vegetable oils; insoluble in water and in glycerin. In solid form, may be dispersible in water.

Vitamin E: Practically odorless and tasteless. The alpha tocopherols and alpha tocopheryl acetates occur as clear, yellow, or greenish yellow, viscous oils. *d*-Alpha tocopheryl acetate may solidify in the cold. Alpha tocopheryl acid succinate occurs as a white powder; the *d*-isomer melts at about 75°, and the *dl*-form melts at about 70°. The alpha tocopherols are unstable to air and light, particularly when in alkaline media. The esters are stable to air and light, but are unstable to alkali; the acid succinate is also unstable when held molten. Alpha tocopheryl acid succinate is very soluble in chloroform; soluble in alcohol, in ether, in acetone, and in vegetable oils; slightly soluble in alkaline solutions; insoluble in water. The other forms of Vitamin E are insoluble in water; soluble in alcohol; miscible with ether, with acetone, with vegetable oils, and with chloroform.

Vitamin E Preparation: The liquid forms are clear, yellow to brownish red, viscous oils. The solid forms are white to tan-white granular powders. The liquid forms are soluble in alcohol; insoluble in water. Miscible with ether, with acetone, with vegetable oils, and with chloroform. The solid forms disperse in water to give cloudy suspensions.

Voriconazole: White to almost white powder. Freely soluble in acetone and in methylene chloride; very slightly soluble in water.

Warfarin Sodium: White, odorless, amorphous or crystalline powder, having a slightly bitter taste. Is discolored by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

Water for Injection: Clear, colorless, odorless liquid. *NF category:* Solvent.

Bacteriostatic Water for Injection: Clear, colorless liquid, odorless or having the odor of the antimicrobial substance. *NF category:* Vehicle (sterile).

Sterile Water for Inhalation: Clear, colorless solution.

Sterile Water for Injection: Clear, colorless, odorless liquid. *NF category:* Solvent.

Sterile Water for Irrigation: Clear, colorless, odorless liquid. *NF category:* Solvent.

Purified Water: Clear, colorless, odorless liquid. *NF category:* Solvent.

Carnauba Wax: Light brown to pale yellow, moderately coarse powder or flakes, possessing a characteristic bland odor, and free from rancidity. Specific gravity is about 0.99. Freely soluble in warm benzene; soluble in warm chloroform and in warm toluene; slightly soluble in boiling alcohol; insoluble in water. *NF category:* Coating agent.

Emulsifying Wax: Creamy white, wax-like solid, having a mild, characteristic odor. Freely soluble in ether, in chloroform, in most hydrocarbon solvents, and in aerosol propellants; soluble in alcohol; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; stiffening agent.

Microcrystalline Wax: White or cream-colored, odorless, waxy solid. Soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils; sparingly soluble in dehydrated alcohol; insoluble in water. *NF category:* Coating agent.

White Wax: Yellowish-white solid, somewhat translucent in thin layers. Has a faint, characteristic odor, and is free from rancidity. Specific gravity is about 0.95. Sparingly soluble in cold alcohol; insoluble in water. Boiling alcohol dissolves the cerotic acid and a portion of the myricin, which are constituents of White Wax. Completely soluble in chloroform, in ether, and in fixed and volatile oils. Partly soluble in cold benzene and in cold carbon disulfide; completely soluble in these liquids at about 30°. *NF category:* Stiffening agent.

Yellow Wax: Solid varying in color from yellow to grayish brown. Has an agreeable, honey-like odor. Is somewhat brittle when cold, and presents a dull, granular, noncrystalline fracture when broken. It becomes pliable from the heat of the hand. Specific gravity is about 0.95. Sparingly soluble in cold alcohol; insoluble in water. Boiling alcohol dissolves the cerotic acid and a portion of the myricin, that are constituents of Yellow Wax. Soluble in chloroform, in ether, in fixed oils, and in volatile oils; sparingly soluble in cold benzene and in cold carbon disulfide; soluble in these liquids at about 30°. *NF category:* Stiffening agent.

Wheat Bran: Light tan powder having a characteristic aroma. Practically insoluble in cold water and in alcohol. Available in a variety of particle sizes depending upon the degree of milling to which it is subjected. Color and flavor development variable, depending on the extent to which it is heat-stabilized.

Xanthan Gum: Cream-colored powder. Its solutions in water are neutral to litmus. Soluble in hot or cold water. *NF category:* Suspending and/or viscosity-increasing agent.

Xenon Xe 127: Clear, colorless gas.

Xenon Xe 133 Injection: Clear, colorless solution.

Xylazine: Colorless to white crystals. Sparingly soluble in dilute acid, in acetone, and in chloroform; insoluble in dilute alkali.

Xylazine Hydrochloride: Colorless to white crystals. Sparingly soluble in dilute acid, in acetone, and in methanol; insoluble in dilute alkali.

Xylitol: White crystals or crystalline powder. It has a sweet taste and produces a cooling sensation in the mouth. One g dissolves in about 0.65 mL of water. Sparingly soluble in alcohol. Crystalline xylitol has a melting range between 92° and 96°.

Xylometazoline Hydrochloride: White to off-white, odorless, crystalline powder. Melts above 300°, with decom-

position. Freely soluble in alcohol; soluble in water; sparingly soluble in chloroform; practically insoluble in benzene and in ether.

Xylose: Colorless needles or white, crystalline powder. Is odorless, and has a slightly sweet taste. Very soluble in water; slightly soluble in alcohol.

Yellow Fever Vaccine: Slightly dull, light-orange colored, flaky or crustlike, desiccated mass.

Yohimbine Hydrochloride: White to yellow powder. Melts at about 295°, with decomposition. Soluble in boiling water; slightly soluble in water and in alcohol.

Yttrium Chloride: Colorless, deliquescent crystals. Soluble in water and in alcohol.

Zalcitabine: White to off-white, crystalline powder. Soluble in water and in methanol; sparingly soluble in alcohol, in acetonitrile, in chloroform, and in methylene chloride; slightly soluble in cyclohexane.

Zaleplon: White to off-white powder. Sparingly soluble in alcohol; slightly soluble in propylene glycol; practically insoluble in water.

Zein: White to yellow powder. Soluble in aqueous alcohols, in glycols, in ethylene glycol ethyl ether, in furfuryl alcohol, in tetrahydrofurfuryl alcohol, in aqueous alkaline solutions of pH 11.5 or greater, and in acetone-water mixtures between the limits of 60% and 80% of acetone by volume; insoluble in water, in acetone, and in all anhydrous alcohols except methanol. *NF category:* Coating agent.

Zidovudine: White to yellowish powder. Melts at about 124°. Exhibits polymorphism. Soluble in alcohol; sparingly soluble in water.

Zileuton: White to off-white powder.

Zinc Acetate: White crystals or granules, having a slight acetous odor and an astringent taste. Is slightly efflorescent. Freely soluble in water and in boiling alcohol; slightly soluble in alcohol.

Zinc Chloride: White or practically white, odorless, crystalline powder, or white or practically white crystalline granules. May also be in porcelain-like masses or molded into cylinders. Is very deliquescent. A solution (1 in 10) is acid to litmus. Very soluble in water; freely soluble in alcohol and in glycerin. Its solution in water or in alcohol is usually slightly turbid, but the turbidity disappears when a small quantity of hydrochloric acid is added.

Zinc Gluconate: White or practically white powder or granules. Soluble in water; very slightly soluble in alcohol.

Zinc Oxide: Very fine, odorless, amorphous, white or yellowish white powder, free from gritty particles. It gradually absorbs carbon dioxide from air. Soluble in dilute acids; insoluble in water and in alcohol.

Zinc Stearate: Fine, white, bulky powder, free from grittiness. Has a faint, characteristic odor. Is neutral to moistened litmus paper. Insoluble in water, in alcohol, and in ether. *NF category:* Tablet and/or capsule lubricant.

Zinc Sulfate: Colorless, transparent prisms, or small needles. May occur as a white, granular, crystalline powder. Is odorless and is efflorescent in dry air. Its solutions are acid to litmus. Very soluble in water (heptahydrate); freely soluble in water (monohydrate) and in glycerin (heptahydrate); practically insoluble in alcohol (monohydrate); insoluble in alcohol (heptahydrate).

Zinc Undecylenate: Fine, white powder. Practically insoluble in water and in alcohol.

Ziprasidone Hydrochloride: White to slightly pink powder. Very soluble in methanol; slightly soluble in isopropyl alcohol, and in hot tetrahydrofuran; practically insoluble in water.

Zolazepam Hydrochloride: White to off-white, crystalline powder. Freely soluble in water and in 0.1 N hydrochloric acid; soluble in methanol; slightly soluble in chloroform; practically insoluble in ether.

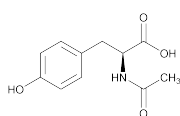
Zolpidem Tartrate: White to off-white powder, hygroscopic. Sparingly soluble in methanol; slightly soluble in water; practically insoluble in methylene chloride.

Zonisamide: White to off-white powder. Freely soluble in dimethylformamide; soluble in methanol.

Dietary Supplements

Official Monographs

N-Acetyltyrosine



$C_{11}H_{13}NO_4$ 223.2
N-Acetyl-L-tyrosine;
(2S)-2-(Acetylamino)-3-(4-hydroxyphenyl)propanoic acid
[537-55-3].

DEFINITION

N-Acetyltyrosine contains NLT 98.5% and NMT 101.0% of N-acetyltyrosine ($C_{11}H_{13}NO_4$), as N-acetyl-L-tyrosine, calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** <197K>
- **B. OPTICAL ROTATION**, *Specific Rotation* <781S>
Sample solution: 10 mg/mL
Acceptance criteria: NLT +46.0° and NMT +49.0°, determined at 20°
- **C.** The R_f value of the principal spot of the *Sample solution* in the test for *Organic Impurities* corresponds to that of *Standard solution 1*.

ASSAY

PROCEDURE

Sample solution: Dissolve about 180 mg of N-Acetyltyrosine, weighed, in 50 mL of carbon dioxide-free water.

Titrimetric system

(See *Titrimetry* <541>.)

Mode: Direct titration

Titrant: 0.1 N sodium hydroxide VS

Endpoint detection: Potentiometric

Equivalency: Each mL of 0.1 N sodium hydroxide VS is equivalent to 22.32 mg of N-acetyltyrosine ($C_{11}H_{13}NO_4$).

IMPURITIES

- **RESIDUE ON IGNITION** <281>: NMT 0.1%
- **CHLORIDE AND SULFATE**, *Chloride* <221>
Sample: 0.7 g
Standard: 0.40 mL of 0.01 N hydrochloric acid
Acceptance criteria: NMT 200 ppm
- **CHLORIDE AND SULFATE**, *Sulfate* <221>
Sample: 1.2 g
Standard: 0.25 mL of 0.020 N sulfuric acid
Acceptance criteria: NMT 200 ppm
- **IRON** <241>: NMT 20 ppm
- **HEAVY METALS**, *Method 1* <231>: NMT 10 ppm

Change to read:

ORGANIC IMPURITIES

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Standard stock solution 1: 8 mg/mL of USP N-Acetyl-L-tyrosine RS in a mixture of water, glacial acetic acid, and alcohol (3:3:94)

Standard solution 1: Dilute *Standard stock solution 1* with alcohol to obtain a solution having a known concentration of about 0.4 mg/mL.

Standard solution 2: 0.8 mg/mL of USP L-Tyrosine RS dissolved in a mixture of glacial acetic acid and water (1:1), and diluted with alcohol

Sample solution: Transfer 0.8 g of N-Acetyltyrosine to a 10-mL volumetric flask, dissolve in 6 mL of a mixture of glacial acetic acid and water (1:1), and dilute with alcohol to volume.

Application volume: 5 μ L

Developing solvent system: A mixture of ammonia and 2-propanol (3:7)

Spray reagent: Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butanol and 2 N acetic acid (95:5).

Analysis: Proceed as directed for *Chromatography* <621>, *Thin-Layer Chromatography*. After air-drying the plate, repeat the development process. After air-drying a second time, ■examine the plate under short-wave UV light, and record principal and secondary spots. ■1S (USP36) Spray the plate with *Spray reagent*, and heat between 100° and 105° for about 15 min. ■Examine the plate under white light, and record the principal and secondary spots. ■1S (USP36)

Acceptance criteria: ■Under the short-wave UV light, ■1S (USP36) any secondary spot observed from the *Sample solution* is not larger or more intense than the principal spot from *Standard solution 1*. ■After applying the *Spray reagent*, under white light, any secondary spot at the locus of tyrosine from the *Sample solution* is not larger or more intense than the principal spot from *Standard solution 2*. ■1S (USP36)

Individual impurities: NMT 0.5%
Limit of tyrosine: NMT 1.0%

SPECIFIC TESTS• **LOSS ON DRYING** (731)

Analysis: Dry a sample at 105° for 3 h.
Acceptance criteria: NMT 0.1%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS** (11)
USP N-Acetyl-L-tyrosine RS
USP L-Tyrosine RS

Add the following:

•Gymnema**DEFINITION**

Gymnema consists of the dried leaves of *Gymnema sylvestre* (Retz.) R. Br. ex Schult. (Fam. Asclepiadaceae). It contains NLT 1.0% of gymnemic acids, calculated as gymnemagenin on the dried basis.

IDENTIFICATION

- **A.** Meets the requirements for *Specific Tests, Botanic Characteristics*

• **B. THIN-LAYER CHROMATOGRAPHY**

Standard solution A: 0.5 mg/mL of USP Gymnemagenin RS in methanol

Standard solution B: 20 mg/mL of USP Native Gymnema Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: About 0.5 g of Gymnema, finely powdered, in 5 mL of methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 5m (HPTLC plates)

Application volume: 5 µL as 8-mm bands

Relative humidity: Condition the plate to a relative humidity of about 33%, using a suitable device.

Developing solvent system: A mixture of dichloromethane, methanol, and formic acid (75:25:10)

Developing distance: 6 cm

Derivatization reagent: A mixture of methanol and sulfuric acid (9:1)

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*. Apply the samples as bands to a suitable high-performance thin-layer chromatographic plate, and dry in air (see *Chromatography* (621)). Develop the chromatograms in a saturated chamber, remove the plate from the chamber, dry in air, derivatize the plate with *Derivatization reagent*, heat at 110 for 3 min, and examine under visible light and UV at 366 nm.

System suitability: The chromatogram of *Standard solution B* shows two bands clearly separated at an R_f of about 0.6–0.7 below the band due to gymnemagenin in *Standard solution A*, and the most prominent band is located at about one-third of the chromatogram, visible as brown in color under white light and blue under UV.

Acceptance criteria: The chromatogram of the *Sample solution* shows the following bands corresponding in color and position to bands in the chromatogram of

Standard solution B: two bands at an R_f of about 0.6–0.7, below the band due to gymnemagenin in *Standard solution A*; the most prominent band at about one-third of the chromatogram, visible as brown in color under white light and blue under UV; and in the lower third of the chromatogram, under UV, one light blue-greenish band and a dark band underneath.

• **C. HPLC**

Analysis: Proceed as directed in the test for *Content of Gymnemic Acids*.

Acceptance criteria: The chromatogram of the *Sample solution* shows a major peak at a retention time corresponding to that of the gymnemagenin peak in the chromatogram of *Standard solution A* and an additional peak corresponding to deacylgymnemic acid.

COMPOSITION• **CONTENT OF GYMNEMIC ACIDS**

Solution A: Dissolve 0.14 g of anhydrous potassium dihydrogen phosphate in 900 mL of water, and add 0.5 mL of phosphoric acid. Dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	45	55
25	40	60
30	40	60
35	75	25
40	75	25

Solvent: 50% ethanol in water

Potassium hydroxide solution: 12% potassium hydroxide in water

Hydrochloric acid solution: 4 N hydrochloric acid

Standard solution A: 0.3 mg/mL of USP Gymnemagenin RS in methanol

Standard solution B: Transfer about 0.25 g of USP Native Gymnema Extract RS to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, transfer to a 50-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45-µm or finer pore size, discarding the first few mL of the filtrate.

Sample solution: Transfer about 0.75 g of Gymnema, finely powdered and accurately weighed, to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, filter into a 100-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45-µm or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-μm, 100 Å, packing L1

Column temperature: 25 ± 1°

Flow rate: 1.6 mL/min

Injection volume: 20 μL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram from *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Native Gymnema Extract RS being used.

Tailing factor: NMT 1.5 for the gymnemagenin peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the gymnemagenin peak, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Using the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Native Gymnema Extract RS being used, identify the retention times of the peaks corresponding to deacylgymnemic acid and gymnemagenin from the *Sample solution*.

Calculate the percentage of gymnemic acids, calculated as gymnemagenin, in the portion of Gymnema taken:

$$\text{Result} = (r_U/r_S) \times C_S \times (V/W) \times 100$$

r_U = peak area of gymnemagenin from the *Sample solution*

r_S = peak area of gymnemagenin from *Standard solution A*

C_S = concentration of gymnemagenin in *Standard solution A* (mg/mL)

V = final volume of the *Sample solution* (mL)

W = weight of Gymnema used to prepare the *Sample solution* (mg)

Acceptance criteria: NLT 1.0% on the dried basis

CONTAMINANTS

- **HEAVY METALS**, *Method III* <231>: NMT 20 μg/g
- **ARTICLES OF BOTANICAL ORIGIN**, *General Method for Pesticide Residues Analysis* <561>: Meets the requirements
- **MICROBIAL ENUMERATION TESTS** <2021>: The total aerobic bacterial count does not exceed 10⁵ cfu/g, the total combined molds and yeasts count does not exceed 10³ cfu/g, and the bile-tolerant Gram-negative bacteria does not exceed 10³ cfu/g.
- **ABSENCE OF SPECIFIED MICROORGANISMS** <2022>: Meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*

SPECIFIC TESTS

• BOTANIC CHARACTERISTICS

Macroscopic: Leaves opposite; petiolate; simple, elliptic or ovate, acute apex, margin entire, acute to acuminate at base; reticulate venation; pubescent on both surfaces, the dorsal surface is more pubescent; about 2–6 cm long, 1–4 cm broad; upper surface is yellowish-brown, lower surface is dark green; bitter taste, when chewed has the property of paralyzing the sense of taste for a few hours for both sweet and bitter substances and in particular sweet substances. Pharmacopoeial article consists of dry, brittle, and green to yellowish-green leaves.

Microscopic

Transverse section of petiole: Horse-shoe shaped. Trichomes present profusely all over the periphery, and are uniseriate, multicellular and thick walled. A layer of epidermis, thick walled cells; 4–5 layers of collenchymatous cortex; and inner parenchyma. The vascular bundles occur as an arc in the middle, three in num-

ber—two small lateral, and one large median. The median bundle consists of xylem elements arranged in radial rows, surrounded by phloem. Xylem consists of vessel elements, tracheids, and fibers. Rosette crystals are present in the collenchyma and parenchyma cells, with more in the cells toward the center. The starch grains are polygonal, simple or compound, in two to many in groups, hilum indistinct.

Transverse section of lamina: Upper and lower epidermal cells, thin wall, covered with thin striated cuticle. Trichomes are present on both surfaces, uniseriate, uni- to tricellular, and thick walled. A single layer of palisade below the upper epidermis occupies one-third of the thickness of the lamina, followed by 3–5 layers of parenchyma cells with large intercellular spaces.

Transverse section of midrib: Upper and lower epidermal cells, thin wall, covered with thin striated cuticle. Trichomes are present, uniseriate, uni- to tricellular, and thick walled, followed by 4–5 layers of compact parenchyma cells on both sides of the midrib; collateral vascular bundles are present, forming an arc shape.

• **ARTICLES OF BOTANICAL ORIGIN**, *Foreign Organic Matter* <561>: NMT 2.0%

• **ARTICLES OF BOTANICAL ORIGIN**, *Alcohol-Soluble Extractives*, *Method I* <561>: NLT 20%

• **ARTICLES OF BOTANICAL ORIGIN**, *Water-Soluble Extractives*, *Method I* <561>: NLT 20%

• LOSS ON DRYING <731>

Sample: 1.0 g of finely powdered Gymnema

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 7.0%

• **ARTICLES OF BOTANICAL ORIGIN**, *Total Ash* <561>

Sample: 1.0 g of finely powdered Gymnema

Acceptance criteria: NMT 15%

• **ARTICLES OF BOTANICAL ORIGIN**, *Acid-Insoluble Ash* <561>

Sample: 1.0 g of finely powdered Gymnema

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light and moisture. Store at room temperature.
- **LABELING:** The label states the Latin binomial and, following the official name, the part of the plant contained in the article.
- **USP REFERENCE STANDARDS** <11>
USP Gymnemagenin RS
USP Native Gymnema Extract RS_{NIS} (USP36)

Add the following:

Native Gymnema Extract

DEFINITION

Native Gymnema Extract is prepared from Gymnema using hydroalcoholic mixtures. The ratio of plant material to extract is about 8:1. It contains NLT 5.0% of gymnemic acids, calculated as gymnemagenin on the dried basis.

IDENTIFICATION

• A. THIN-LAYER CHROMATOGRAPHY

Standard solution A: 0.5 mg/mL of USP Gymnemagenin RS in methanol

Standard solution B: 20 mg/mL of USP Native Gymnema Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: 20 mg/mL of Native Gymnema Extract in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 5 µm (HPTLC plates)

Application volume: 5 µL as 8-mm bands

Relative humidity: Condition the plate to a relative humidity of about 33%, using a suitable device.

Developing solvent system: A mixture of dichloromethane, methanol, and formic acid (75:25:10)

Developing distance: 6 cm

Derivatization reagent: A mixture of methanol and sulfuric acid (9:1)

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*. Apply the samples as bands to a suitable high-performance thin-layer chromatographic plate, and dry in air (see *Chromatography* (621)). Develop the chromatograms in a saturated chamber, remove the plate from the chamber, dry in air, derivatize the plate with *Derivatization reagent*, heat at 110° for 3 min, and examine under visible light and UV at 366 nm.

System suitability: The chromatogram of *Standard solution B* shows two bands clearly separated at an R_f of about 0.6–0.7 below the band due to gymnemagenin in *Standard solution A*, and the most prominent band is located at about one-third of the chromatogram, visible as brown in color under white light and blue under UV.

Acceptance criteria: The chromatogram of the *Sample solution* shows the following bands corresponding in color and position to bands in the chromatogram of *Standard solution B*: two bands at an R_f of about 0.6–0.7, below the band due to gymnemagenin in *Standard solution A*; the most prominent band at about one-third of the chromatogram, visible as brown in color under white light and blue under UV; and in the lower third of the chromatogram, under UV, one light blue-greenish band and a dark band underneath.

B. HPLC

Analysis: Proceed as directed in the test for *Content of Gymnemic Acids*.

Acceptance criteria: The chromatogram of the *Sample solution* shows a major peak at a retention time corresponding to that of the gymnemagenin peak in the chromatogram of *Standard solution A* and an additional peak corresponding to deacylgymnemic acid.

COMPOSITION**• CONTENT OF GYMNEMIC ACIDS**

Solution A: Dissolve 0.14 g of anhydrous potassium dihydrogen phosphate in 900 mL of water, and add 0.5 mL of phosphoric acid. Dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	45	55
25	40	60
30	40	60
35	75	25
40	75	25

Solvent: 50% ethanol in water

Potassium hydroxide solution: 12% potassium hydroxide in water

Hydrochloric acid solution: 4 N hydrochloric acid

Standard solution A: 0.3 mg/mL of USP Gymnemagenin RS in methanol

Standard solution B: Transfer about 0.25 g of USP Native Gymnema Extract RS to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, transfer to a 50-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45-µm or finer pore size, discarding the first few mL of the filtrate.

Sample solution: Transfer an amount of Native Gymnema Extract, equivalent to about 30 mg of gymnemic acids, to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, transfer to a 100-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45-µm or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm, 100 Å, packing L1

Column temperature: 25 ± 1°

Flow rate: 1.6 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram from *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Native Gymnema Extract RS being used.

Tailing factor: NMT 1.5 for the gymnemagenin peak, *Standard solution A*

Relative standard deviation: NMT 2.0% determined from the gymnemagenin peak in repeated injections, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Using the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Native Gymnema Extract RS being used, identify the retention times of the peaks corresponding to deacylgymnemic acid and gymnemagenin from the *Sample solution*.

Calculate the percentage of gymnemic acids, calculated as gymnemagenin, in the portion of Native Gymnema Extract taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of gymnemagenin from the *Sample solution*

r_S = peak area of gymnemagenin from *Standard solution A*

C_S = concentration of gymnemagenin in *Standard solution A* (mg/mL)

C_U = concentration of Native Gymnema Extract in the *Sample solution* (mg/mL)

Acceptance criteria: NLT 5.0% on the dried basis

CONTAMINANTS

• **HEAVY METALS**, *Method III* (231): NMT 20 µg/g

• **ARTICLES OF BOTANICAL ORIGIN**, *General Method for Pesticide Residues Analysis* (561): Meets the requirements

- **MICROBIAL ENUMERATION TESTS** (2021): The total aerobic bacterial count does not exceed 10^4 cfu/g, and the total combined molds and yeasts count does not exceed 10^3 cfu/g.
- **ABSENCE OF SPECIFIED MICROORGANISMS** (2022): Meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

SPECIFIC TESTS

- **LOSS ON DRYING** (731)
Sample: 1.0 g of Native Gymnema Extract
Analysis: Dry at 105° for 3 h.
Acceptance criteria: NMT 5.0%
- **ARTICLES OF BOTANICAL ORIGIN, Total Ash** (561)
Sample: 1.0 g of Native Gymnema Extract
Acceptance criteria: NMT 8%
- **ARTICLES OF BOTANICAL ORIGIN, Acid-Insoluble Ash** (561)
Sample: 1.0 g of Native Gymnema Extract
Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light and moisture. Store at controlled room temperature.
- **LABELING:** The label states the Latin binomial and, following the official name, the part of the plant from which the article was derived. It meets other labeling requirements under *Botanical Extracts* (565).
- **USP REFERENCE STANDARDS** (11)
USP Gymnemagenin RS
USP Native Gymnema Extract RS_{11S} (USP36)

Add the following:

Powdered Gymnema

DEFINITION

Powdered Gymnema is Gymnema reduced to powder or very fine powder. It contains NLT 1.0% of gymnemic acids, calculated as gymnemagenin on the dried basis.

IDENTIFICATION

- **A.** Meets the requirements for *Specific Tests, Botanic Characteristics*.
- **B. THIN-LAYER CHROMATOGRAPHY**
Standard solution A: 0.5 mg/mL of USP Gymnemagenin RS in methanol
Standard solution B: 20 mg/mL of USP Native Gymnema Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.
Sample solution: About 0.5 g of Powdered Gymnema in 5 mL of methanol. Sonicate for 10 min, centrifuge, and use the supernatant.
Chromatographic system
Adsorbent: Chromatographic silica gel mixture with an average particle size of 5 μ m (HPTLC plates)
Application volume: 5 μ L as 8-mm bands
Relative humidity: Condition the plate to a relative humidity of about 33%, using a suitable device.
Developing solvent system: A mixture of dichloromethane, methanol, and formic acid (75:25:10)
Developing distance: 6 cm
Derivatization reagent: A mixture of methanol and sulfuric acid (9:1)
Analysis
Samples: Standard solution A, Standard solution B, and Sample solution. Apply the samples as bands to a suitable high-performance thin-layer chromatographic plate, and dry in air (see *Chromatography* (621)). Develop the chromatograms in a saturated chamber, re-

move the plate from the chamber, dry in air, derivatize the plate with *Derivatization reagent*, heat at 110° for 3 min, and examine under visible light and UV at 366 nm.

System suitability: The chromatogram of *Standard solution B* shows two bands clearly separated at an R_f of about 0.6–0.7 below the band due to gymnemagenin in *Standard solution A*, and the most prominent band is located at about one-third of the chromatogram, visible as brown in color under white light and blue under UV.

Acceptance criteria: The chromatogram of the *Sample solution* shows the following bands corresponding in color and position to bands in the chromatogram of *Standard solution B*: two bands at an R_f of about 0.6–0.7, below the band due to gymnemagenin in *Standard solution A*; the most prominent band at about one-third of the chromatogram, visible as brown in color under white light and blue under UV; and in the lower third of the chromatogram, under UV, one light blue-greenish band and a dark band underneath.

C. HPLC

Analysis: Proceed as directed in the test for *Content of Gymnemic Acids*.

Acceptance criteria: The chromatogram of the *Sample solution* shows a major peak at a retention time corresponding to that of the gymnemagenin peak in the chromatogram of *Standard solution A* and an additional peak corresponding to deacylgymnemic acid.

COMPOSITION

CONTENT OF GYMNEMIC ACIDS

Solution A: Dissolve 0.14 g of anhydrous potassium dihydrogen phosphate in 900 mL of water, and add 0.5 mL of phosphoric acid. Dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	45	55
25	40	60
30	40	60
35	75	25
40	75	25

Solvent: 50% ethanol in water

Potassium hydroxide solution: 12% potassium hydroxide in water

Hydrochloric acid solution: 4 N hydrochloric acid

Standard solution A: 0.3 mg/mL of USP

Gymnemagenin RS in methanol

Standard solution B: Transfer about 0.25 g of USP Native Gymnema Extract RS to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, transfer to a 50-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45- μ m or finer pore size, discarding the first few mL of the filtrate.

Sample solution: Transfer about 0.75 g of Powdered Gymnema, accurately weighed, to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature.

Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, filter into a 100-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45- μ m or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm \times 25-cm; 5- μ m, 100 Å, packing L1

Column temperature: 25 \pm 1°

Flow rate: 1.6 mL/min

Injection volume: 20 μ L

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram from *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Native *Gymnema Extract RS* being used.

Tailing factor: NMT 1.5 for the gymnemagenin peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the gymnemagenin peak, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Using the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Native *Gymnema Extract RS* being used, identify the retention times of the peaks corresponding to deacylgymnemic acid and gymnemagenin from the *Sample solution*.

Calculate the percentage of gymnemic acids, calculated as gymnemagenin, in the portion of Powdered *Gymnema* taken:

$$\text{Result} = (r_u/r_s) \times C_s \times (V/W) \times 100$$

r_u = peak area of gymnemagenin from the *Sample solution*

r_s = peak area of gymnemagenin from *Standard solution A*

C_s = concentration of gymnemagenin in *Standard solution A* (mg/mL)

V = final volume of the *Sample solution* (mL)

W = weight of Powdered *Gymnema* used to prepare the *Sample solution* (mg)

Acceptance criteria: NLT 1.0% on the dried basis

CONTAMINANTS

- **HEAVY METALS**, *Method III* (231): NMT 20 μ g/g
- **ARTICLES OF BOTANICAL ORIGIN**, *General Method for Pesticide Residues Analysis* (561): Meets the requirements
- **MICROBIAL ENUMERATION TESTS** (2021): The total aerobic bacterial count does not exceed 10⁵ cfu/g, the total combined molds and yeasts count does not exceed 10³ cfu/g, and the bile-tolerant Gram-negative bacteria does not exceed 10³ cfu/g.
- **ABSENCE OF SPECIFIED MICROORGANISMS** (2022): Meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*

SPECIFIC TESTS

BOTANICAL CHARACTERISTICS

Microscopic

Under a microscope, it shows fragments of upper and lower epidermal cells, polygonal, thin and straight walls, covered with striated cuticle, anomocytic stomata; trichomes are present on both surfaces, uniseriate, uni- to tricellular, and thick walled; fragments of collenchyma and parenchyma cells, some containing

rosettes of calcium oxalate; starch grains, polygonal, simple or compound, hilum indistinct; fragments of reticulate and spiral vessels, and tracheids.

• **ARTICLES OF BOTANICAL ORIGIN**, *Alcohol-Soluble Extractives*, *Method I* (561): NLT 20%

• **ARTICLES OF BOTANICAL ORIGIN**, *Water-Soluble Extractives*, *Method I* (561): NLT 20%

LOSS ON DRYING (731)

Sample: 1.0 g of Powdered *Gymnema*

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 7.0%

• **ARTICLES OF BOTANICAL ORIGIN**, *Total Ash* (561)

Sample: 1.0 g of Powdered *Gymnema*

Acceptance criteria: NMT 15%

• **ARTICLES OF BOTANICAL ORIGIN**, *Acid-Insoluble Ash* (561)

Sample: 1.0 g of Powdered *Gymnema*

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light and moisture. Store at room temperature.

• **LABELING:** The label states the Latin binomial and, following the official name, the part of the plant used to prepare the article.

USP REFERENCE STANDARDS (11)

USP Gymnemagenin RS

USP Native *Gymnema Extract RS*_{1S} (USP36)

Add the following:

Purified *Gymnema Extract*

DEFINITION

Purified *Gymnema Extract* is prepared from Native *Gymnema Extract* by precipitation using dilute hydrochloric acid solution. The ratio of plant material to extract is about 25:1. It contains NLT 90.0% and NMT 110.0% of the labeled amount of gymnemic acids, calculated as gymnemagenin on the dried basis. It may contain suitable added substances as carriers.

IDENTIFICATION

A. THIN-LAYER CHROMATOGRAPHY

Standard solution A: 0.5 mg/mL of USP

Gymnemagenin RS in methanol

Standard solution B: 20 mg/mL of USP Native

Gymnema Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: 20 mg/mL of Purified *Gymnema Extract* in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 5 μ m (HPTLC plates)

Application volume: 5 μ L as 8-mm bands

Relative humidity: Condition the plate to a relative humidity of about 33%, using a suitable device.

Developing solvent system: A mixture of dichloromethane, methanol, and formic acid (75:25:10)

Developing distance: 6 cm

Derivatization reagent: A mixture of methanol and sulfuric acid (9:1)

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*. Apply the samples as bands to a suitable high-performance thin-layer chromatographic plate, and dry in air (see *Chromatography* (621)). Develop the chromatograms in a saturated chamber, remove the plate from the chamber, dry in air, deriva-

tize the plate with *Derivatization reagent*, heat at 110° for 3 min, and examine under visible light and UV at 366 nm.

System suitability: The chromatogram of *Standard solution B* shows two bands clearly separated at an R_f of about 0.6–0.7 below the band due to gymnemagenin in *Standard solution A*, and the most prominent band is located at about one-third of the chromatogram, visible as brown in color under white light and blue under UV.

Acceptance criteria: The chromatogram of the *Sample solution* shows the following bands corresponding in color and position to bands in the chromatogram of *Standard solution B*: two bands at an R_f of about 0.6–0.7, below the band due to gymnemagenin in *Standard solution A*; the most prominent band at about one-third of the chromatogram, visible as brown in color under white light and blue under UV; and in the lower third of the chromatogram, under UV, one light blue-greenish band and a dark band underneath.

• B. HPLC

Analysis: Proceed as directed in the test for *Content of Gymnemic Acids*.

Acceptance criteria: The chromatogram of the *Sample solution* shows a major peak at a retention time corresponding to that of the gymnemagenin peak in the chromatogram of *Standard solution A* and an additional peak corresponding to deacylgymnemic acid.

COMPOSITION

• CONTENT OF GYMNEMIC ACIDS

Solution A: Dissolve 0.14 g of anhydrous potassium dihydrogen phosphate in 900 mL of water, and add 0.5 mL of phosphoric acid. Dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
20	45	55
25	40	60
30	40	60
35	75	25
40	75	25

Solvent: 50% ethanol in water

Potassium hydroxide solution: 12% potassium hydroxide in water

Hydrochloric acid solution: 4 N hydrochloric acid

Standard solution A: 0.3 mg/mL of USP

Gymnemagenin RS in methanol

Standard solution B: Transfer about 0.25 g of USP Native Gymnema Extract RS to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, transfer to a 50-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45-μm or finer pore size, discarding the first few mL of the filtrate.

Sample solution: Transfer an amount of Purified Gymnema Extract, equivalent to about 30 mg of gymnemic acids, to a 100-mL round-bottom flask fitted with a reflux condenser. Add 25 mL of *Solvent* and 2 mL

of *Potassium hydroxide solution*, reflux on a water bath for 1 h, and cool to room temperature. Add 5.5 mL of *Hydrochloric acid solution*, reflux on a water bath for 2 h, and cool to room temperature. Adjust the solution with *Potassium hydroxide solution* to a pH of 7.5–8.5, transfer to a 100-mL volumetric flask, dilute with *Solvent* to volume, and mix. Before injection, pass through a membrane filter having a 0.45-μm or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-μm, 100 Å, packing L1

Column temperature: 25 ± 1°

Flow rate: 1.6 mL/min

Injection volume: 20 μL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram from *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Native Gymnema Extract RS being used.

Tailing factor: NMT 1.5 for the gymnemagenin peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the gymnemagenin peak, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Using the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Native Gymnema Extract RS being used, identify the retention times of the peaks corresponding to deacylgymnemic acid and gymnemagenin in the *Sample solution* chromatogram. Calculate the percentage (P) of gymnemic acids, calculated as gymnemagenin, in the portion of Purified Gymnema Extract taken:

$$P = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of gymnemagenin from the *Sample solution*

r_S = peak area of gymnemagenin from *Standard solution A*

C_S = concentration of gymnemagenin in *Standard solution A* (mg/mL)

C_U = concentration of Purified Gymnema Extract in the *Sample solution* (mg/mL)

Calculate the percentage of the labeled amount of gymnemic acids in the portion of Purified Gymnema Extract taken:

$$\text{Result} = (P/L) \times 100$$

P = content of gymnemic acids as determined above (%)

L = labeled amount of gymnemic acids (%)

Acceptance criteria: 90%–110% of the labeled amount

CONTAMINANTS

• **HEAVY METALS, Method III (231):** NMT 20 μg/g

• **ARTICLES OF BOTANICAL ORIGIN, General Method for Pesticide Residues Analysis (561):** Meets the requirements

• **MICROBIAL ENUMERATION TESTS (2021):** The total aerobic bacterial count does not exceed 10⁴ cfu/g, and the total combined molds and yeasts count does not exceed 10³ cfu/g.

• **ABSENCE OF SPECIFIED MICROORGANISMS (2022):** Meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*

SPECIFIC TESTS• **LOSS ON DRYING** (731)

Sample: 1.0 g of Purified *Gymnema* Extract

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 5.0%

• **ARTICLES OF BOTANICAL ORIGIN, Total Ash** (561)

Sample: 1.0 g of Purified *Gymnema* Extract

Acceptance criteria: NMT 8%

• **ARTICLES OF BOTANICAL ORIGIN, Acid-Insoluble Ash** (561)

Sample: 1.0 g of Purified *Gymnema* Extract

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light and moisture. Store at controlled room temperature.

• **LABELING:** The label states the Latin binomial and, following the official name, the part of the plant from which the article was derived. Label it to indicate the content of gymnemic acids, in percentage. It meets other labeling requirements under *Botanical Extracts* (565).

• **USP REFERENCE STANDARDS** (11)

USP *Gymnemagenin* RS

USP Native *Gymnema* Extract RS^{1S} (USP36)

Valerian

DEFINITION**Change to read:**

Valerian consists of the subterranean parts of *Valeriana officinalis* L. (Fam. Valerianaceae) including the rhizome, roots, and stolons. It contains NLT 0.5% of volatile oil, NLT 0.05% of valerenic acid (C₁₅H₂₂O₂), and NLT 0.17% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid, on the dried basis. ^{1S} (USP36)

IDENTIFICATION**Change to read:**

• **A.** ^{1S} Meets the requirements for *Specific Tests, Botanic Characteristics*. ^{1S} (USP36)

Change to read:

• **B.**
Sample solution: 0.2 g of freshly powdered Valerian in 5 mL of methylene chloride. Shake several times, and allow to stand for 5 min. Filter, wash the filter with 2 mL of methylene chloride, combine the filtrate and washings, and evaporate to dryness. Dissolve the residue in 0.2 mL of methylene chloride.

Analysis: To 0.1 mL of the *Sample solution* add 3 mL of a mixture of equal volumes of glacial acetic acid and 25% hydrochloric acid, and shake several times.

Acceptance criteria: A blue color develops within 15 min. ^{1S} (USP36)

Add the following:• **C. THIN-LAYER CHROMATOGRAPHY**

Standard solution A: 0.25 mg/mL of USP Valerenic Acid RS in methanol

Standard solution B: 40 mg/mL of USP Powdered Valerian Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: About 0.5 g of Valerian, finely powdered, in 5 mL of methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 2–10 µm (HPTLC plates)

Application volume: 5 µL, as 8-mm bands

Developing solvent system: A mixture of cyclohexane, ethyl acetate, and acetic acid (60:38:2)

Derivatization reagent A: A mixture of glacial acetic acid and hydrochloric acid (1:4)

Derivatization reagent B: 0.5 mL of *p*-anisaldehyde, 10 mL of acetic acid, and 5 mL of sulfuric acid. Add to 85 mL of ice-cold methanol, and mix.

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Apply the *Samples* as bands to a suitable high-performance thin-layer chromatographic plate. Use a saturated chamber, and condition the plate to a relative humidity of about 33% using a suitable device. Develop the chromatograms over a distance of 6 cm. Remove the plate from the chamber, dry, derivatize with *Derivatization reagent A*, heat at 120° for 5 min, and examine under white light. Derivatize with *Derivatization reagent B*, heat at 100° for 3 min, and examine under white light.

Acceptance criteria: After treatment with *Derivatization reagent A* and heating, the *Sample solution* does not exhibit an intense blue band at about the middle of the chromatogram nor any other significant bands [distinction from Mexican valerian (*Valeriana edulis*)], though minor bands may be observed.

After treatment with *Derivatization reagent B* and heating, the *Sample solution* exhibits three violet bands in positions and colors similar to the bands of *Standard solution B*. These bands include a minor band in the lower third of the chromatogram due to hydroxyvalerenic acid, a major band at about the middle the chromatogram due to acetoxyvalerenic acid [distinction from Scouler's valerian (*Valeriana wallichii*)], and a major band at an *R_f* corresponding to the valerenic acid band of *Standard solution A* and *Standard solution B*. Other minor bands may be observed in the *Sample solution* and in *Standard solution B*. ^{1S} (USP36)

Add the following:• **D. HPLC**

Analysis: Proceed as directed in the test for *Content of Valerenic Acids*.

Acceptance criteria: The *Sample solution* exhibits a peak at a retention time corresponding to the valerenic acid peak of *Standard solution A*. The *Sample solution* shows additional peaks corresponding to hydroxyvalerenic acid and acetoxyvalerenic acid. ^{1S} (USP36)

COMPOSITION**Change to read:**• **CONTENT OF VALERENIC ACIDS** ^{1S} (USP36)

Solution A: Mix 6 mL of 85% phosphoric acid with 900 mL of water, dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Mix 6 mL of 85% phosphoric acid with 900 mL of methanol, dilute with methanol to 1000 mL, mix, filter, and degas.

Mobile phase: See Table 1.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	40	60
15	5	95
25	5	95
30	40	60

Solvent: A mixture of methanol and a solution of 0.1% phosphoric acid in water (3:1)

Standard solution A: 0.02 mg/mL of USP Valerenic Acid RS in methanol. Sonicate if necessary.

Standard solution B: Sonicate a portion of USP Powdered Valerian Extract RS in *Solvent* to obtain a solution having a concentration of about 20 mg/mL. Before injection, pass through a membrane filter of 0.45-μm or finer pore size, discarding the first few mL of the filtrate.

Sample solution: To a 50-mL volumetric flask, transfer about 1.0 g of Valerian, finely powdered and accurately weighed, add 10.0 mL of water, and shake for 2 min while heating in a water bath maintained at about 50°. Sonicate for 15 min, add 35 mL of methanol, and sonicate for 15 min. Cool, dilute with methanol to volume, and mix. Before injection, pass through a membrane filter of 0.45-μm or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; end-capped, 5-μm 100 Å packing L1

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 25 μL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram of *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Tailing factor: NMT 2.0 for the valerenic acid peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the valerenic acid peak in repeated injections, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Identify the valerenic acids in the *Sample solution* chromatogram by comparison with the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Calculate the percentages of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid in the portion of Valerian taken:

$$\text{Result} = (r_u/r_s) \times C_s \times (V/W) \times F \times 100$$

r_u = peak area of the relevant analyte from the *Sample solution*

r_s = peak area of valerenic acid from *Standard solution A*

C_s = concentration of valerenic acid in *Standard solution A* (mg/mL)

V = volume of the *Sample solution* (mL)

W = weight of Valerian taken to prepare the *Sample solution* (mg)

F = conversion factor for each analyte (1.10 for hydroxyvalerenic acid, 1.25 for acetoxyvalerenic acid, and 1.00 for valerenic acid)

Acceptance criteria: NLT 0.05% of valerenic acid ($C_{15}H_{22}O_2$), and NLT 0.17% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid on the dried basis¹⁵ (USP36)

ARTICLES OF BOTANICAL ORIGIN, Volatile Oil Determination <561>

Sample: 100 g, freshly and coarsely comminuted

Acceptance criteria: NLT 0.5% on the dried basis

CONTAMINANTS

Add the following:

ELEMENTAL IMPURITIES—PROCEDURES <233>

Acceptance criteria

Arsenic: NMT 0.5 μg/g

Cadmium: NMT 1.0 μg/g

Lead: NMT 5.0 μg/g

Mercury: NMT 0.1 μg/g¹⁵ (USP36)

ARTICLES OF BOTANICAL ORIGIN, General Method for Pesticide Residues Analysis <561>

Meets the requirements

MICROBIAL ENUMERATION TESTS <2021>

The total bacterial count does not exceed 10⁵ cfu/g, the total combined molds and yeasts count does not exceed 10³ cfu/g, and bile-tolerant Gram-negative bacteria does not exceed 10³ cfu/g.

ABSENCE OF SPECIFIED MICROORGANISMS <2022>

It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

SPECIFIC TESTS

Change to read:

BOTANIC CHARACTERISTICS

Macroscopic: Rhizomes: yellowish-gray to pale grayish-brown; entire or cut longitudinally; up to 5 cm in length and up to 3 cm in diameter; base elongated or compressed, covered by and merging with numerous roots; apices usually bearing a cup-shaped scar from aerial parts, stem base rarely present, fracture reveals pith with a central cavity, transverse septum observed in longitudinal cut. Roots: yellowish-gray to pale grayish-brown with longitudinal stripes, numerous, cylindrical, slender, about 10 cm in length and up to 3 mm in diameter, a few filiform, fragile secondary roots, fracture short. Stolons: pale yellowish-gray, showing prominent nodes separated by longitudinally striated internodes each 2–5 cm in length, fracture fibrous.

Microscopic: Roots: epidermis, pilliferous layer with papillose cells, some developed into root hairs and exodermis consisting of a single layer of quadrangular to polygonal cells with suberized walls; oil globules scattered through the epidermis and cortex; cortex, occupying most of the root, outer part consisting of 2–4 layers of resin-containing cells, inner part consisting of numerous layers of polygonal to subrounded cells filled with starch granules, clefts present; endodermis consisting of a single layer of slightly lignified cells, Caspary dots distinct; pericycle consisting of 1–2 layers of tangentially elongated cells, sometimes indistinct; phloem, vascular bundles forming an interrupted ring; cambium frequently indistinct; xylem, continuously distributed, with polygonal vessels, surrounding a central pith; pith showing cells with slightly thickened walls containing starch granules; starch granules, simple, hilum dotted, stellate or cleft-shaped, 5–15 μm in diameter; compound starch granules of 2–6 components. Rhizomes: similar to roots except epidermis and exodermis par-

tially replaced by poorly developed periderm; presence of numerous vascular bundles; central pith wider, including clefts of various sizes, the larger being separated by groups of stone cells. ■^{1S} (USP36)

- **ARTICLES OF BOTANICAL ORIGIN, Foreign Organic Matter** (561): NMT 2.0%

- **EXTRACTABLE MATTER**

Sample: 2 g, carefully dried at 40° and coarsely powdered

Analysis: Mix the *Sample* with 20 mL of 70% alcohol, and allow to stand for 2 h, shaking frequently. Filter, evaporate 5 mL of the filtrate on a water bath to dryness, and dry the residue at 105°.

Acceptance criteria: NLT 20%

Delete the following:

- **ARTICLES OF BOTANICAL ORIGIN, Water Content** (561): NMT 12.0% ■^{1S} (USP36)

Add the following:

- **LOSS ON DRYING** (731)
Sample: 1.0 g of finely powdered Valerian
Analysis: Dry at 105° for 2 h.
Acceptance criteria: NMT 12% ■^{1S} (USP36)
- **ARTICLES OF BOTANICAL ORIGIN, Total Ash** (561): NMT 12.0%
- **ARTICLES OF BOTANICAL ORIGIN, Acid-Insoluble Ash** (561): NMT 5.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, store at room temperature, and protect from light and moisture.
- **LABELING:** The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

Change to read:

- **USP REFERENCE STANDARDS** (11)
■ USP Powdered Valerian Extract RS ■^{1S} (USP36)
USP Valerenic Acid RS

Valerian Tablets

DEFINITION

Change to read:

Valerian Tablets contain Powdered Valerian Extract. Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of Powdered Valerian Extract, ■ calculated as valerenic acids equivalent to the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid. ■^{1S} (USP36)

IDENTIFICATION

Delete the following:

- **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** (201)
Standard solution: 0.5 mg/mL each of USP Fluorescein RS and USP Valerenic Acid RS in methanol
Sample solution: Transfer an equivalent to 100 mg of Powdered Valerian Extract from finely powdered Tablets (NLT 10) to a suitable flask. Add 5 mL of water and

3 mL of a 10% aqueous solution of potassium hydroxide, extract this mixture with two 5-mL portions of methylene chloride, and discard the organic phase. Heat the aqueous phase in a water bath at 40° for 10 min, cool, acidify with 7% hydrochloric acid, and extract this solution with two 5-mL portions of methylene chloride. Dry the organic phase over anhydrous sodium sulfate, filter, evaporate the filtrate to dryness, and dissolve the residue in 1.0 mL of methylene chloride.

Adsorbent: 0.5-mm layer of chromatographic silica gel mixture

Application volume

Standard solution: 10 µL

Sample solution: 20 µL, in a 2-cm band

Developing solvent system: Solvent hexane, ethyl acetate, and glacial acetic acid (65:35:0.5)

Spray reagent: Mix 0.5 mL of anisaldehyde with 10 mL of glacial acetic acid, 85 mL of methanol, and 5 mL of sulfuric acid, added in the sequence specified.

Analysis

Samples: *Standard solution* and *Sample solution*

Spray the plate with *Spray reagent*. Heat the plate in an oven at 105° for 10 min, and examine the plate under white light.

Acceptance criteria: The *Standard solution* chromatogram shows a violet zone due to valerenic acid at an R_F value of 0.4, and a yellow zone due to fluorescein at an R_F value of 0.1. The *Sample solution* chromatogram shows a violet zone due to valerenic acid at an R_F value of 0.4, and a blue-violet zone due to hydroxyvalerenic acid at an R_F value of 0.12, just above the yellow zone in the *Standard solution*. The *Sample solution* chromatogram may show other colored zones at R_F values lower than those of valerenic acid. ■^{1S} (USP36)

Add the following:

- **A. THIN-LAYER CHROMATOGRAPHY**

Standard solution A: 0.25 mg/mL of USP Valerenic Acid RS in methanol

Standard solution B: 40 mg/mL of USP Powdered Valerian Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: Finely pulverize NLT 10 Tablets.

Transfer an amount of the powder equivalent to 100 mg of Powdered Valerian Extract to a suitable flask. Add 5 mL of water and 3 mL of a 10% aqueous solution of potassium hydroxide, extract with two 5-mL portions of methylene chloride, and discard the organic phase. Heat the aqueous phase in a water bath at 40° for 10 min, cool, acidify with 7% hydrochloric acid, and extract with two 5-mL portions of methylene chloride. Dry the organic phase over anhydrous sodium sulfate, filter, evaporate the filtrate to dryness, and dissolve the residue in 2.0 mL of methylene chloride.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 2–10 µm (HPTLC plates)

Application volume: 5 µL, as 8-mm bands

Developing solvent system: A mixture of cyclohexane, ethyl acetate, and acetic acid (60:38:2)

Derivatization reagent A: A mixture of glacial acetic acid and hydrochloric acid (1:4)

Derivatization reagent B: 0.5 mL of *p*-anisaldehyde, 10 mL of acetic acid, and 5 mL of sulfuric acid. Add to 85 mL of ice-cold methanol, and mix.

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Apply the *Samples* as bands to a suitable high-performance thin-layer chromatographic plate. Use a saturated chamber, and condition the plate to a relative humidity of about 33% using a suitable device. Develop the chromatograms over a distance of 6 cm. Re-

move the plate from the chamber, dry, derivatize with *Derivatization reagent A*, heat at 120° for 5 min, and examine under white light. Derivatize with *Derivatization reagent B*, heat at 100° for 3 min, and examine under white light.

Acceptance criteria: After treatment with *Derivatization reagent A* and heating, the *Sample solution* does not exhibit an intense blue band at about the middle of the chromatogram nor any other significant bands [distinction from Mexican valerian (*Valeriana edulis*)], though minor bands may be observed.

After treatment with *Derivatization reagent B* and heating, the *Sample solution* exhibits three violet bands in positions and colors similar to the bands of *Standard solution B*. These bands include a minor band in the lower third of the chromatogram due to hydroxyvalerenic acid, a major band at about the middle of the chromatogram due to acetoxyvalerenic acid [distinction from Scouler's valerian (*Valeriana wallichii*)], and a major band at an R_f corresponding to the valerenic acid band of *Standard solution A* and *Standard solution B*. Other minor bands may be observed in the *Sample solution* and in *Standard solution B*. ■1S (USP36)

Change to read:

• B. ■HPLC ■1S (USP36)

■Analysis: Proceed as directed in the test for *Content of Valerenic Acids*.

Acceptance criteria: The *Sample solution* exhibits a peak at a retention time corresponding to the valerenic acid peak of *Standard solution A*. The *Sample solution* shows additional peaks corresponding to hydroxyvalerenic acid and acetoxyvalerenic acid. ■1S (USP36)

STRENGTH

Delete the following:

• CONTENT OF VALERENIC ACID

Mobile phase: Methanol and water (77:27). Add 0.5 mL of phosphoric acid to each 100 mL of the mixture.

System suitability solution: 24 µg/mL of USP Valerenic Acid RS in methanol

Standard solution: 3.5 µg/mL of USP Valerenic Acid RS in methanol

Sample solution: Weigh NLT 20 Tablets, and pulverize with a mortar and pestle. Transfer a portion of the powder, nominally equivalent to 0.09 mg of valerenic acid, to a suitable flask. Add 25.0 mL of methanol, shake to disperse the powder, sonicate for 10 min, and centrifuge. Use the clear supernatant.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Capacity factor, k' : NLT 5, determined from valerenic acid

Tailing factor: NMT 2.0 for valerenic acid

Relative standard deviation: NMT 2.0% for valerenic acid

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of Extract as valerenic acid in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S \times V/W) \times (100/L_E) \times (A_W \times 100/L)$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Valerenic Acid RS in the *Standard solution* (mg/mL)

V = volume of the *Sample solution* (mL)

W = weight of the sample of powdered Tablets used to prepare the *Sample solution* (mg)

A_W = average weight of the Tablets (mg/Tablet)

L_E = labeled amount of valerenic acid in 100 mg of the Extract used to prepare the Tablets (mg)

L = labeled amount of Extract per Tablet (mg/Tablet)

Acceptance criteria: 90.0%–120.0% ■1S (USP36)

Add the following:

• CONTENT OF VALERIAN EXTRACT

Solution A: Mix 6 mL of 85% phosphoric acid with 900 mL of water, dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Mix 6 mL of 85% phosphoric acid with 900 mL of methanol, dilute with methanol to 1000 mL, mix, filter, and degas.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	40	60
15	5	95
25	5	95
30	40	60

Solvent: A mixture of methanol and a solution of 0.1% phosphoric acid in water (3:1)

Standard solution A: 0.02 mg/mL of USP Valerenic Acid RS in methanol. Sonicate if necessary.

Standard solution B: Sonicate a portion of USP Powdered Valerian Extract RS in *Solvent* to obtain a solution having a concentration of about 20 mg/mL. Before injection, pass through a membrane filter of 0.45-µm or finer pore size, discarding the first few mL of the filtrate.

Sample solution: Weigh NLT 20 Tablets and pulverize. Transfer a portion of the powder, nominally equivalent to about 3.0 mg of valerenic acids, to a suitable flask. Add 25.0 mL of *Solvent*, shake to disperse the powder, sonicate for 10 min, and centrifuge. Use the clear supernatant.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; end-capped, 5-µm 100 Å packing L1

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 25 µL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram of *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Tailing factor: NMT 2.0 for the valerenic acid peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the valerenic acid peak in repeated injections, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Identify the valerenic acids in the *Sample solution* chromatogram by comparison with the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Calculate the percentage of the labeled amount of Powdered Valerian Extract as valerenic acids (sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid) in the portion of Tablets taken:

$$\text{Result} = \left\{ \left[\sum (r_u \times F) \right] / r_s \right\} \times (C_s \times V/W) \times (100/L_E) \times (A_W \times 100/L)$$

- r_u = peak areas of the relevant analytes from the *Sample solution*
- F = conversion factor for each analyte (1.10 for hydroxyvalerenic acid, 1.25 for acetoxyvalerenic acid, and 1.00 for valerenic acid)
- r_s = peak area of valerenic acid from *Standard solution A*
- C_s = concentration of valerenic acid in *Standard solution A* (mg/mL)
- V = volume of the *Sample solution* (mL)
- W = weight of the sample of powdered Tablets used to prepare the *Sample solution* (mg)
- A_W = average weight of the Tablets (mg/Tablet)
- L_E = labeled amount of valerenic acids in 100 mg of the Powdered Valerian Extract used to prepare the Tablets (mg)
- L = labeled amount of Powdered Valerian Extract per Tablet (mg/Tablet)

Acceptance criteria: 90.0%–120.0% ■^{1S} (USP36)

PERFORMANCE TESTS

- **DISINTEGRATION AND DISSOLUTION OF DIETARY SUPPLEMENTS** <2040>: Meet the requirements for *Disintegration*
- **WEIGHT VARIATION OF DIETARY SUPPLEMENTS** <2091>: Meet the requirements

CONTAMINANTS

- **MICROBIAL ENUMERATION TESTS** <2021>: The total aerobic microbial count does not exceed 10^4 cfu/g, and the total combined molds and yeasts count does not exceed 10^3 cfu/g.
- **MICROBIAL PROCEDURES FOR ABSENCE OF SPECIFIED MICROORGANISMS** <2022>: Meet the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at room temperature.

Change to read:

- **LABELING:** The label states the Latin binomial and, following the official name, the article from which the Tablets

were prepared. The label also indicates the quantity, in mg, of Powdered Valerian Extract per Tablet and the content, ■as a percentage, of valerenic acids in the Extract. ■^{1S} (USP36)

Change to read:• **USP REFERENCE STANDARDS** <11>

- USP Powdered Valerian Extract RS ■^{1S} (USP36)
- USP Valerenic Acid RS

Powdered Valerian**DEFINITION****Change to read:**

Powdered Valerian is Valerian reduced to a fine or a very fine powder. It contains no calcium oxalate crystals and no foreign starch granules. It contains NLT 0.3% of volatile oil, NLT 0.04% of valerenic acid ($C_{15}H_{22}O_2$), ■and NLT 0.1% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid, on the dried basis. ■^{1S} (USP36)

IDENTIFICATION**Change to read:**

- **A.** ■Meets the requirements for *Specific Tests, Botanic Characteristics* ■^{1S} (USP36)

Change to read:

- **B.**
 - Sample solution:** 0.2 g of Powdered Valerian in 5 mL of methylene chloride. Shake several times, and allow to stand for 5 min. Filter, wash the filter with 2 mL of methylene chloride, combine the filtrate and washings, and evaporate to dryness. Dissolve the residue in 0.2 mL of methylene chloride.
 - Analysis:** To 0.1 mL of the *Sample solution* add 3 mL of a mixture of equal volumes of glacial acetic acid and 25% hydrochloric acid, and shake several times.
 - Acceptance criteria:** A blue color develops within 15 min. ■^{1S} (USP36)

Add the following:• **C. THIN-LAYER CHROMATOGRAPHY**

Standard solution A: 0.25 mg/mL of USP Valerenic Acid RS in methanol

Standard solution B: 40 mg/mL of USP Powdered Valerian Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: About 0.5 g of Powdered Valerian in 5 mL of methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 2–10 μ m (HPTLC plates)

Application volume: 5 μ L, as 8-mm bands

Developing solvent system: A mixture of cyclohexane, ethyl acetate, and acetic acid (60:38:2)

Derivatization reagent A: A mixture of glacial acetic acid and hydrochloric acid (1:4)

Derivatization reagent B: 0.5 mL of *p*-anisaldehyde, 10 mL of acetic acid, and 5 mL of sulfuric acid. Add to 85 mL of ice-cold methanol, and mix.

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Apply the *Samples* as bands to a suitable high-performance thin-layer chromatographic plate. Use a saturated chamber, and condition the plate to a relative humidity of about 33% using a suitable device. Develop the chromatograms over a distance of 6 cm. Remove the plate from the chamber, dry, derivatize with *Derivatization reagent A*, heat at 120° for 5 min, and examine under white light. Derivatize with *Derivatization reagent B*, heat at 100° for 3 min, and examine under white light.

Acceptance criteria: After treatment with *Derivatization reagent A* and heating, the *Sample solution* does not exhibit an intense blue band at about the middle of the chromatogram nor any other significant bands [distinction from Mexican valerian (*Valeriana edulis*)], though minor bands may be observed.

After treatment with *Derivatization reagent B* and heating, the *Sample solution* exhibits three violet bands in positions and colors similar to the bands of *Standard solution B*. These bands include a minor band in the lower third of the chromatogram due to hydroxyvalerenic acid, a major band at about the middle the chromatogram due to acetoxyvalerenic acid [distinction from Scouler's valerian (*Valeriana wallichii*)], and a major band at an R_f corresponding to the valerenic acid band of *Standard solution A* and *Standard solution B*. Other minor bands may be observed in the *Sample solution* and in *Standard solution B*.^{■1S (USP36)}

Add the following:

■ D. HPLC

Analysis: Proceed as directed in the test for *Content of Valerenic Acids*.

Acceptance criteria: The *Sample solution* exhibits a peak at a retention time corresponding to the valerenic acid peak of *Standard solution A*. The *Sample solution* shows additional peaks corresponding to hydroxyvalerenic acid and acetoxyvalerenic acid.^{■1S (USP36)}

COMPOSITION

Change to read:

■ CONTENT OF VALERENIC ACIDS^{■1S (USP36)}

Solution A: Mix 6 mL of 85% phosphoric acid with 900 mL of water, dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Mix 6 mL of 85% phosphoric acid with 900 mL of methanol, dilute with methanol to 1000 mL, mix, filter, and degas.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	40	60
15	5	95
25	5	95
30	40	60

Solvent: A mixture of methanol and a solution of 0.1% phosphoric acid in water (3:1)

Standard solution A: 0.02 mg/mL of USP Valerenic Acid RS in methanol. Sonicate if necessary.

Standard solution B: Sonicate a portion of USP Powdered Valerian Extract RS in *Solvent* to obtain a solution having a concentration of about 20 mg/mL. Before injection, pass through a membrane filter of 0.45-μm or finer pore size, discarding the first few mL of the filtrate.

Sample solution: To a 50-mL volumetric flask, transfer about 1.0 g of Powdered Valerian, accurately weighed, add 10.0 mL of water, and shake for 2 min while heating in a water bath maintained at about 50°. Sonicate for 15 min, add 35 mL of methanol, and sonicate for 15 min. Cool, dilute with methanol to volume, and mix. Before injection, pass through a membrane filter of 0.45-μm or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; end-capped, 5-μm 100 Å packing L1

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 25 μL

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram of *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Tailing factor: NMT 2.0 for the valerenic acid peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the valerenic acid peak in repeated injections, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Identify the valerenic acids in the *Sample solution* chromatogram by comparison with the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Calculate the percentages of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid in the portion of Powdered Valerian taken:

$$\text{Result} = (r_U/r_S) \times C_S \times (V/W) \times F \times 100$$

r_U = peak area of the relevant analyte from the *Sample solution*

r_S = peak area of valerenic acid from *Standard solution A*

C_S = concentration of valerenic acid in *Standard solution A* (mg/mL)

V = volume of the *Sample solution* (mL)

W = weight of Powdered Valerian taken to prepare the *Sample solution* (mg)

F = conversion factor for each analyte (1.10 for hydroxyvalerenic acid, 1.25 for acetoxyvalerenic acid, and 1.00 for valerenic acid)

Acceptance criteria: NLT 0.04% of valerenic acid ($C_{15}H_{22}O_2$), and NLT 0.1% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetox-valerenic acid, and valerenic acid on the dried basis. ■1S (USP36)

• **ARTICLES OF BOTANICAL ORIGIN, Volatile Oil Determination** (561)

Sample: 100 g of Powdered Valerian
Acceptance criteria: NLT 0.3%

CONTAMINANTS

Delete the following:

- **HEAVY METALS** (231): 50 µg/g. ■1S (USP36)

Add the following:

- **ELEMENTAL IMPURITIES—PROCEDURES** (233)

Acceptance criteria

Arsenic: NMT 0.5 µg/g

Cadmium: NMT 1.0 µg/g

Lead: NMT 5.0 µg/g

Mercury: NMT 0.1 µg/g. ■1S (USP36)

- **ARTICLES OF BOTANICAL ORIGIN, General Method for Pesticide Residues Analysis** (561): Meets the requirements
- **MICROBIAL ENUMERATION TESTS** (2021): The total bacterial count does not exceed 10^5 cfu/g, the total combined molds and yeasts count does not exceed 10^3 cfu/g, and bile-tolerant Gram-negative bacteria does not exceed 10^3 cfu/g.
- **ABSENCE OF SPECIFIED MICROORGANISMS** (2022): It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

SPECIFIC TESTS

Change to read:

- **BOTANIC CHARACTERISTICS**

Microscopic: ■Numerous starch granules, simple, hilum dotted, stellate or cleft-shaped, 5–15 µm in diameter; compound starch granules of 2–6 components; black, cruciate shape under a polarizing microscope. Scattered stone cells, single or aggregated, with cell lumina of various sizes, bright yellowish-white or bright white under a polarizing microscope; numerous fragments of parenchyma cells containing globules of volatile oil and starch granules; fragments of pale yellow lignified fibers, scattered, single or aggregated; fragments of vessels, reticulate, bordered pitted and spiral. ■1S (USP36)

Delete the following:

- **ARTICLES OF BOTANICAL ORIGIN, Foreign Organic Matter** (561): NMT 2.0%. ■1S (USP36)

- **EXTRACTABLE MATTER**

Sample: 2 g of Powdered Valerian, carefully dried at 40°

Analysis: Mix the *Sample* with 20 mL of 70% alcohol, and allow to stand for 2 h, shaking frequently. Filter, evaporate 5 mL of the filtrate on a water bath to dryness, and dry the residue at 105°.

Acceptance criteria: NLT 20%

Delete the following:

- **WATER, Method 1a** (921): NMT 5.0%. ■1S (USP36)

Add the following:

- **LOSS ON DRYING** (731)

Sample: 1.0 g of Powdered Valerian

Analysis: Dry at 105° for 2 h.

Acceptance criteria: NMT 12%. ■1S (USP36)

- **ARTICLES OF BOTANICAL ORIGIN, Total Ash** (561): NMT 12.0%
- **ARTICLES OF BOTANICAL ORIGIN, Acid-Insoluble Ash** (561): NMT 5.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, store at room temperature, and protect from light and moisture.
- **LABELING:** The label states the Latin binomial and, following the official name, the parts of the plant from which the article was derived.

Change to read:

- **USP REFERENCE STANDARDS** (11)

■USP Powdered Valerian Extract RS. ■1S (USP36)

USP Valerenic Acid RS

Powdered Valerian Extract

DEFINITION

Change to read:

- Powdered Valerian Extract is prepared from comminuted Valerian using hydroalcoholic mixtures. It contains NLT 0.3% of valerenic acid ($C_{15}H_{22}O_2$), and NLT 0.6% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetox-valerenic acid, and valerenic acid, on the dried basis. The ratio of the starting crude plant material to the Extract is between 4:1 and 7:1. ■1S (USP36)

IDENTIFICATION

Delete the following:

- **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST**

Standard solution: 0.5 mg/mL each of USP Fluorescein RS and USP Valerenic Acid RS, in methanol

Sample solution: Dissolve 0.2 g of Extract in 2 mL of water, add 3 mL of a 10% aqueous solution of potassium hydroxide, and extract this mixture with two 5-mL portions of methylene chloride. Discard the organic phase, heat the aqueous phase on a water bath at 40° for 10 min, cool, acidify with 7% hydrochloric acid, and extract this solution with two 5-mL portions of methylene chloride. Dry the organic phase over anhydrous sodium sulfate, and filter. Evaporate the filtrate to dryness, and dissolve the residue in 1.0 mL of methylene chloride.

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Adsorbent: 0.5-mm layer of chromatographic silica gel mixture

Application volume

Standard solution: 10 μ L

Sample solution: 20 μ L

Developing solvent system: Solvent hexane, ethyl acetate, and glacial acetic acid (65: 35: 0.5)

Spray reagent: Mix 0.5 mL of anisaldehyde with 10 mL of glacial acetic acid, 85 mL of methanol, and 5 mL of sulfuric acid, added in the sequence specified.

Analysis

Samples: *Standard solution* and *Sample solution*

Spray the plate with *Spray reagent*. Heat the plate in an oven at 105° for 10 min, and examine the plate under white light.

Acceptance criteria: The *Standard solution* chromatogram shows a violet zone due to valerenic acid at an R_f value of 0.4, and a yellow zone due to fluorescein at an R_f value of 0.1. The *Sample solution* chromatogram shows a violet zone due to valerenic acid at an R_f value of 0.4, and a blue-violet zone due to hydroxyvalerenic acid at an R_f value of 0.12, just above the yellow zone in the *Standard solution*. The chromatogram of the *Sample solution* may show other colored zones at R_f values lower than those of valerenic acid. ■1S (USP36)

Add the following:**• A. THIN-LAYER CHROMATOGRAPHY**

Standard solution A: 0.25 mg/mL of USP Valerenic Acid RS in methanol

Standard solution B: 40 mg/mL of USP Powdered Valerian Extract RS in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Sample solution: 40 mg/mL of Extract in methanol. Sonicate for 10 min, centrifuge, and use the supernatant.

Chromatographic system

Adsorbent: Chromatographic silica gel mixture with an average particle size of 2–10 μ m (HPTLC plates)

Application volume: 5 μ L, as 8-mm bands

Developing solvent system: A mixture of cyclohexane, ethyl acetate, and acetic acid (60:38:2)

Derivatization reagent A: A mixture of glacial acetic acid and hydrochloric acid (1:4)

Derivatization reagent B: 0.5 mL of *p*-anisaldehyde, 10 mL of acetic acid, and 5 mL of sulfuric acid. Add to 85 mL of ice-cold methanol, and mix.

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Apply the *Samples* as bands to a suitable high-performance thin-layer chromatographic plate. Use a saturated chamber, and condition the plate to a relative humidity of about 33% using a suitable device. Develop the chromatograms over a distance of 6 cm. Remove the plate from the chamber, dry, derivatize with *Derivatization reagent A*, heat at 120° for 5 min, and examine under white light. Derivatize with *Derivatization reagent B*, heat at 100° for 3 min, and examine under white light.

Acceptance criteria: After treatment with *Derivatization reagent A* and heating, the *Sample solution* does not exhibit an intense blue band at about the middle of the chromatogram nor any other significant bands [distinction from Mexican valerian (*Valeriana edulis*)], though minor bands may be observed.

After treatment with *Derivatization reagent B* and heating, the *Sample solution* exhibits three violet bands in positions and colors similar to the bands of *Standard solution B*. These bands include a minor band in the

lower third of the chromatogram due to hydroxyvalerenic acid, a major band at about the middle the chromatogram due to acetoxyvalerenic acid [distinction from Scouler's valerian (*Valeriana wallichii*)], and a major band at an R_f corresponding to the valerenic acid band of *Standard solution A* and *Standard solution B*. Other minor bands may be observed in the *Sample solution* and in *Standard solution B*. ■1S (USP36)

Change to read:**• B. HPLC**

Analysis: Proceed as directed in the test for *Content of Valerenic Acids*.

Acceptance criteria: The *Sample solution* exhibits a peak at a retention time corresponding to the valerenic acid peak of *Standard solution A*. The *Sample solution* shows additional peaks corresponding to hydroxyvalerenic acid and acetoxyvalerenic acid. ■1S (USP36)

COMPOSITION**Change to read:****• CONTENT OF VALERENIC ACIDS ■1S (USP36)**

Solution A: Mix 6 mL of 85% phosphoric acid with 900 mL of water, dilute with water to 1000 mL, mix, filter, and degas.

Solution B: Mix 6 mL of 85% phosphoric acid with 900 mL of methanol, dilute with methanol to 1000 mL, mix, filter, and degas.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	40	60
15	5	95
25	5	95
30	40	60

Solvent: A mixture of methanol and a solution of 0.1% phosphoric acid in water (3:1)

Standard solution A: 0.05 mg/mL of USP Valerenic Acid RS in methanol. Sonicate if necessary.

Standard solution B: Sonicate a portion of USP Powdered Valerian Extract RS in *Solvent* to obtain a solution having a concentration of about 20 mg/mL. Before injection, pass through a membrane filter of 0.45- μ m or finer pore size, discarding the first few mL of the filtrate.

Sample solution: Sonicate a portion of Extract in *Solvent* to obtain a solution having a concentration of about 20 mg/mL. Before injection, pass through a membrane filter of 0.45- μ m or finer pore size, discarding the first few mL of the filtrate.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm \times 25-cm; end-capped, 5- μ m 100 Å packing L1

Column temperature: 40°

Flow rate: 1.0 mL/min

Injection volume: 25 μ L

System suitability

Samples: *Standard solution A* and *Standard solution B*

Suitability requirements

Chromatogram similarity: The chromatogram of *Standard solution B* is similar to the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Tailing factor: NMT 2.0 for the valerenic acid peak, *Standard solution A*

Relative standard deviation: NMT 2.0% for the valerenic acid peak in repeated injections, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Identify the valerenic acids in the *Sample solution* chromatogram by comparison with the chromatograms of *Standard solution A*, *Standard solution B*, and the reference chromatogram provided with the lot of USP Powdered Valerian Extract RS being used.

Calculate the percentages of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid in the portion of Powdered Valerian Extract taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times F \times 100$$

r_U = peak area of the relevant analyte from the *Sample solution*

r_S = peak area of valerenic acid from *Standard solution A*

C_S = concentration of valerenic acid in *Standard solution A* (mg/mL)

C_U = concentration of the Extract in the *Sample solution* (mg/mL)

F = conversion factor for each analyte (1.10 for hydroxyvalerenic acid, 1.25 for acetoxyvalerenic acid, and 1.00 for valerenic acid)

Acceptance criteria: NLT 0.3% of valerenic acid ($C_{15}H_{22}O_2$), and NLT 0.6% of total valerenic acids, calculated as the sum of hydroxyvalerenic acid, acetoxyvalerenic acid, and valerenic acid on the dried basis ■1S (USP36)

CONTAMINANTS

Add the following:

■ ELEMENTAL IMPURITIES—PROCEDURES <233>

Acceptance criteria

Arsenic: NMT 0.5 µg/g

Cadmium: NMT 1.0 µg/g

Lead: NMT 5.0 µg/g

Mercury: NMT 0.1 µg/g ■1S (USP36)

• ARTICLES OF BOTANICAL ORIGIN, *Pesticide Residues* <561>: Meets the requirements

Delete the following:

■ ALCOHOL DETERMINATION, *Method II* <611>: NMT 2.0%, if present ■1S (USP36)

• **MICROBIAL ENUMERATION TESTS** <2021>: The total bacterial count does not exceed 10^4 cfu/g, the total combined molds and yeasts count does not exceed 10^3 cfu/g, the coliform count does not exceed 10^3 cfu/g, and the *Enterobacteriaceae* count does not exceed 10^3 cfu/g.

• **ABSENCE OF SPECIFIED MICROORGANISMS** <2022>: It meets the requirements of the tests for absence of *Salmonella* species, *Escherichia coli*, and *Staphylococcus aureus*.

SPECIFIC TESTS

• LOSS ON DRYING <731>

Sample: 1.0 g of Extract

Analysis: Dry at 105° for 2 h.

Acceptance criteria: NMT 9%

• ARTICLES OF BOTANICAL ORIGIN, *Total Ash* <561>: NMT 7.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, store at controlled room temperature, and protect from moisture and light.

Change to read:

• **LABELING:** ■The label states the official name of the article, the Latin binomial, and the part of the plant from which the article was prepared. Label it to indicate the content of valerenic acid and total valerenic acids, and the ratio of the starting crude plant material to the Extract. It meets other labeling requirements in *Botanical Extracts* <565>.

■1S (USP36)

Change to read:

• USP REFERENCE STANDARDS <11>

■USP Powdered Valerian Extract RS ■1S (USP36)

USP Valerenic Acid RS

Excipients

USP and NF Excipients, Listed by Category

In the following reference table, the grouping of excipients by functional category is intended to summarize the most typically identified purpose that these excipients serve in drug product formulations. The list of substances included in each category is not comprehensive. The statement of category is intended neither to limit in any way the choice or use of the substance nor to indicate that it has no other utility.

Acidifying Agent

Acetic Acid
Acetic Acid, Glacial
Citric Acid, Anhydrous
Citric Acid Monohydrate
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

Aerosol Propellant

Butane
Dichlorodifluoromethane
Dichlorotetrafluoroethane
Isobutane
Propane
Trichloromonofluoromethane

Air Displacement

Carbon Dioxide
Nitrogen

Alcohol Denaturant

Denatonium Benzoate
Methyl Isobutyl Ketone
Sucrose Octaacetate

Alkalizing Agent

Ammonia Solution, Strong
Ammonium Carbonate
Diethanolamine
Potassium Hydroxide
Sodium Bicarbonate
Sodium Borate
Sodium Carbonate
Sodium Hydroxide
Trolamine

Anticaking Agent (See *Glidant*)

Antifoaming Agent

Dimethicone
Myristic Acid
Palmitic Acid
Simethicone

Antimicrobial Preservative

Benzalkonium Chloride
Benzalkonium Chloride Solution

Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
Calcium Propionate
Cetrimonium Bromide
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Dehydroacetic Acid
Erythorbic Acid
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
Phenoxyethanol
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

Antioxidant

Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Butylated Hydroxytoluene
Erythorbic Acid
Hypophosphorous Acid
Lactobionic Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Racemethionine
Sodium Bisulfite
Sodium Formaldehyde Sulfoxylate
Sodium Metabisulfite
Sodium Sulfite
Sodium Thiosulfate
Stannous Chloride
Sulfur Dioxide
Tocopherols Excipient

Buffering Agent

Acetic Acid
Adipic Acid
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
Citric Acid, Anhydrous

Citric Acid Monohydrate
 Alpha-Lactalbumin
 Lactic Acid
 Phosphoric Acid
 Potassium Citrate
 Potassium Metaphosphate
 Potassium Phosphate, Dibasic
 Potassium Phosphate, Monobasic
 Racemethionine
 Sodium Acetate
 Sodium Citrate
 Sodium Lactate Solution
 Sodium Phosphate, Dibasic
 Sodium Phosphate, Monobasic
 Succinic Acid

Bulking Agent for Freeze-Drying

Creatinine
 Alpha-Lactalbumin
 Mannitol
 Polydextrose
 Polydextrose, Hydrogenated
 Pullulan
 Trehalose

Capsule Lubricant (See *Tablet and/or Capsule Lubricant*)**Chelating Agent**

Edetate Calcium Disodium
 Edetate Disodium
 Edetic Acid

Coating Agent

Amino Methacrylate Copolymer
 Ammonio Methacrylate Copolymer
 Ammonio Methacrylate Copolymer Dispersion
 Carboxymethylcellulose Sodium
 Carboxymethylcellulose Sodium, Enzymatically-Hydrolyzed
 Cellaburate
 Cellacefate (formerly Cellulose Acetate Phthalate)
 Cellulose Acetate
 Cellulose Acetate Phthalate (see Cellacefate)
 Chitosan
 Coconut Oil
 Coconut Oil, Hydrogenated
 Copovidone
 Corn Syrup Solids
 Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion
 Ethylcellulose
 Ethylcellulose Aqueous Dispersion
 Ethylcellulose Dispersion Type B
 Ethylene Glycol and Vinyl Alcohol Graft Copolymer
 Gelatin
 Glaze, Pharmaceutical
 Hydroxypropyl Cellulose
 Hydroxypropyl Methylcellulose (see Hypromellose)
 Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
 Hypromellose (formerly Hydroxypropyl Methylcellulose)
 Hypromellose Acetate Succinate
 Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
 Alpha-Lactalbumin
 Maltodextrin
 Methacrylic Acid and Ethyl Acrylate Copolymer
 Methacrylic Acid and Ethyl Acrylate Copolymer, Partially-Neutralized
 Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion
 Methacrylic Acid and Methyl Methacrylate Copolymer
 Methacrylic Acid Copolymer
 Methacrylic Acid Copolymer Dispersion
 Methylcellulose
 Palm Kernel Oil
 Palm Oil
 Palm Oil, Hydrogenated

Polydextrose, Hydrogenated
 Polyethylene Glycol
 Polyvinyl Acetate
 Polyvinyl Acetate Dispersion
 Polyvinyl Acetate Phthalate
 Pullulan
 Rapeseed Oil, Fully Hydrogenated
 Rapeseed Oil, Superglycerinated Fully Hydrogenated
 Shellac
 Starch, Pregelatinized Modified
 Sucrose
 Titanium Dioxide
 Wax, Carnauba
 Wax, Microcrystalline
 Zein

Color

Caramel
 Ferric Oxide, red, yellow, or blends
 Ferrosoferric Oxide

Coloring Agent

Aluminum Oxide

Complexing Agent

Betadex Sulfobutyl Ether Sodium
 Edetate Calcium Disodium
 Edetate Disodium
 Edetic Acid
 Alpha-Lactalbumin
 Oxyquinoline Sulfate

Desiccant

Calcium Chloride
 Calcium Sulfate
 Polyvinyl Acetate
 Silicon Dioxide

Emollient

Alkyl (C12-15) Benzoate
 Oleyl Oleate
 Polydecene, Hydrogenated
 Soybean Oil, Hydrogenated

Change to read:**Emulsifying and/or Solubilizing Agent**

Acacia
 ■Butyl Palmitostearate■^{1S} (NF31)
 ■Butyl Stearate■^{1S} (NF31)
 ▲Caprylic Acid▲^{NF31}
 Carbomer Copolymer
 Carbomer Interpolymer
 Cholesterol
 Coconut Oil
 Cyclodextrin, Gamma
 Desoxycholic Acid
 Diethanolamine (Adjunct)
 Diethylene Glycol Stearates
 Ethylene Glycol Stearates
 Glyceryl Distearate
 Glyceryl Monolinoleate
 Glyceryl Monooleate
 Glyceryl Monostearate
 ▲Glyceryl Tristearate▲^{NF31}
 Alpha-Lactalbumin
 Lanolin Alcohols
 Lecithin
 Mono- and Di-glycerides
 Monoethanolamine (Adjunct)
 Oleic Acid (Adjunct)
 Oleyl Alcohol (Stabilizer)
 Oleyl Oleate
 Palm Kernel Oil
 Palm Oil
 Poloxamer
 Polyglyceryl 3 Diisostearate
 Polyglyceryl Dioleate

Polyoxyethylene 50 Stearate
 Polyoxyl 10 Oleyl Ether
 Polyoxyl 20 Cetostearyl Ether
 Polyoxyl 35 Castor Oil
 Polyoxyl 40 Hydrogenated Castor Oil
 Polyoxyl 40 Stearate
 Polyoxyl Lauryl Ether
 Polyoxyl Stearyl Ether
 Polysorbate 20
 Polysorbate 40
 Polysorbate 60
 Polysorbate 80
 Polyoxyl Stearate
 Propylene Glycol Dicaprylate/Dicaprate
 Propylene Glycol Monocaprylate
 Propylene Glycol Monostearate
 Rapeseed Oil, Superglycerinated Fully Hydrogenated
 Sodium Cetostearyl Sulfate
 Sodium Lauryl Sulfate
 Sodium Stearate
 Sorbitan Monolaurate
 Sorbitan Monooleate
 Sorbitan Monopalmitate
 Sorbitan Monostearate
 Sorbitan Sesquioleate
 Sorbitan Trioleate
 Stannous Chloride
 Stearic Acid
 Sucrose Stearate
 Trolamine
 Wax, Emulsifying

Film-Forming Agent

Ammonio Methacrylate Copolymer
 Chitosan
 Ethylcellulose Dispersion Type B
 Methacrylic Acid and Ethyl Acrylate Copolymer
 Methacrylic Acid and Ethyl Acrylate Copolymer, Partially-Neutralized
 Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion
 Methacrylic Acid and Methyl Methacrylate Copolymer

Filtering Aid

Cellulose, Powdered
 Siliceous Earth, Purified

Change to read:**Flavors and Perfumes**

Almond Oil
 ■Ammonium Glycyrrhizate■1S (NF31)
 Anethole
 Benzaldehyde
 ■Butyl Palmitostearate■1S (NF31)
 ■Butyl Stearate■1S (NF31)
 ▲Diethyl Sebacate▲NF31
 Ethyl Acetate
 Ethyl Vanillin
 L-Glutamic Acid, Hydrochloride
 Lactitol
 Maltol
 Menthhol
 Methyl Salicylate
 Monosodium Glutamate
 Peppermint
 Peppermint Oil
 Peppermint Spirit
 Racemethionine
 Rose Oil
 Rose Water, Stronger
 Thymol
 Vanillin

Glidant and/or Anticaking Agent

Calcium Silicate
 Magnesium Silicate
 Silica, Hydrophobic Colloidal
 Silicon Dioxide, Colloidal
 Talc

Change to read:**Humectant**

Corn Syrup Solids
 Erythritol
 Glycerin
 Hexylene Glycol
 Inositol
 Maltitol
 Polydextrose
 Polydextrose, Hydrogenated
 ■Propanediol■1S (NF31)
 Propylene Glycol
 Sorbitol
 Sorbitol Sorbitan Solution
 Starch Hydrolysate, Hydrogenated
 Tagatose

Ointment Base

Caprylocaproyl Polyoxylglycerides
 Diethylene Glycol Monoethyl Ether
 Lanolin
 Lauroyl Polyoxylglycerides
 Linoleoyl Polyoxylglycerides
 Ointment, Hydrophilic
 Ointment, White
 Ointment, Yellow
 Oleoyl Polyoxylglycerides
 Petrolatum
 Petrolatum, Hydrophilic
 Petrolatum, White
 Polydecene, Hydrogenated
 Polyethylene Glycol Monomethyl Ether
 Polyglyceryl 3 Diisostearate
 Rose Water Ointment
 Squalane
 Stearoyl Polyoxylglycerides
 Vegetable Oil, Hydrogenated, Type II

Change to read:**Plasticizer**

Acetyltributyl Citrate
 Acetyltriethyl Citrate
 ■Butyl Palmitostearate■1S (NF31)
 ■Butyl Stearate■1S (NF31)
 Castor Oil
 Diacetylated Monoglycerides
 Dibutyl Sebacate
 Diethyl Phthalate
 Glycerin
 Polyethylene Glycol
 Polyethylene Glycol Monomethyl Ether
 Propylene Glycol
 Pullulan
 Sorbitol Sorbitan Solution
 Triacetin
 Tributyl Citrate
 Triethyl Citrate

Polymer Membrane

Amino Methacrylate Copolymer
 Ammonio Methacrylate Copolymer
 Ammonio Methacrylate Copolymer Dispersion

Cellulose Acetate
 Ethyl Acrylate and Methyl Methacrylate Copolymer
 Dispersion
 Pullulan

Sequestering Agent

Betadex (formerly Beta Cyclodextrin)
 Betadex Sulfobutyl Ether Sodium
 Cyclodextrin, Beta (see Betadex)
 Cyclodextrin, Gamma
 Hydroxypropyl Betadex
 Pullulan
 Sodium Tartrate

Change to read:**Solvent**

Acetone
 Alcohol
 Alcohol, Diluted
 Amylene Hydrate
 Benzyl Benzoate
 Butyl Alcohol
 Canola Oil
 Caprylocaproyl Polyoxylglycerides
 Corn Oil
 Cottonseed Oil
 Diethylene Glycol Monoethyl Ether
 Ethyl Acetate
 Glycerin
 Hexylene Glycol
 Isopropyl Alcohol
 Lauroyl Polyoxylglycerides
 Linoleoyl Polyoxylglycerides
 Methyl Alcohol
 Methyl Isobutyl Ketone
 Methylene Chloride
 Methylpyrrolidone
 Mineral Oil
 Oleoyl Polyoxylglycerides
 Peanut Oil
 Polydecene, Hydrogenated
 Polyethylene Glycol
 Polyethylene Glycol Monomethyl Ether
 ■Propanediol■_{1S} (NF31)
 Propylene Glycol
 Sesame Oil
 Stearoyl Polyoxylglycerides
 Water, Purified
 Water for Injection
 Water for Injection, Sterile
 Water for Irrigation, Sterile

Sorbent

Cellulose, Powdered
 Charcoal, Activated
 Siliceous Earth, Purified

Sorbent, Carbon Dioxide

Barium Hydroxide Lime
 Soda Lime

Stiffening Agent

Castor Oil, Hydrogenated
 Cetostearyl Alcohol
 Cetyl Alcohol
 Cetyl Esters Wax
 Cetyl Palmitate
 Hard Fat
 Alpha-Lactalbumin
 Paraffin
 Paraffin, Synthetic
 Rapeseed Oil, Fully Hydrogenated
 Rapeseed Oil, Superglycerinated Fully Hydrogenated
 Stearyl Alcohol
 Wax, Emulsifying

Wax, White
 Wax, Yellow

Suppository Base

Cocoa Butter
 Hard Fat
 Polyethylene Glycol

Suspending and/or Viscosity-Increasing Agent

Acacia
 Agar
 Alamic Acid
 Alginic Acid
 Aluminum Monostearate
 Attapulgate, Activated
 Attapulgate, Colloidal Activated
 Bentonite
 Bentonite, Purified
 Bentonite Magma
 Carbomer 910
 Carbomer 934
 Carbomer 934P
 Carbomer 940
 Carbomer 941
 Carbomer 1342
 Carbomer Copolymer
 Carbomer Homopolymer
 Carbomer Interpolymer
 Carboxymethylcellulose Calcium
 Carboxymethylcellulose Sodium
 Carboxymethylcellulose Sodium 12
 Carboxymethylcellulose Sodium, Enzymatically-Hydrolyzed
 Carmellose
 Carrageenan
 Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
 Chitosan
 Corn Syrup
 Corn Syrup Solids
 Dextrin
 Gelatin
 Gellan Gum
 Guar Gum
 Hydroxyethyl Cellulose
 Hydroxypropyl Cellulose
 Hydroxypropyl Methylcellulose (see Hypromellose)
 Hypromellose (formerly Hydroxypropyl Methylcellulose)
 Alpha-Lactalbumin
 Magnesium Aluminum Silicate
 Maltodextrin
 Methylcellulose
 Pectin
 Polydextrose, Hydrogenated
 Polyethylene Oxide
 Polyvinyl Alcohol
 Povidone
 Propylene Glycol Alginate
 Pullulan
 Silica, Hydrophobic Colloidal
 Silicon Dioxide
 Silicon Dioxide, Colloidal
 Sodium Alginate
 Starch, Corn
 Starch, Hydroxypropyl Corn
 Starch, Pregelatinized Hydroxypropyl Corn
 Starch, Pea
 Starch, Hydroxypropyl Pea
 Starch, Pregelatinized Hydroxypropyl Pea
 Starch, Potato
 Starch, Hydroxypropyl Potato
 Starch, Pregelatinized Hydroxypropyl Potato
 Starch, Tapioca
 Starch, Wheat
 Sucrose Palmitate
 Tragacanth

Xanthan Gum

Sweetening Agent

Acesulfame Potassium
 Aspartame
 Aspartame Acesulfame
 Corn Syrup
 Corn Syrup, High Fructose
 Corn Syrup Solids
 Dextrates
 Dextrose
 Dextrose Excipient
 Erythritol
 Fructose
 Galactose
 Maltitol
 Maltose
 Mannitol
 Saccharin
 Saccharin Calcium
 Saccharin Sodium
 Sorbitol
 Sorbitol Solution
 Starch Hydrolysate, Hydrogenated
 Sucralose
 Sucrose
 Sugar, Compressible
 Sugar, Confectioner's
 Syrup
 Tagatose
 Trehalose

Tablet Binder

Acacia
 Alginic Acid
 Amino Methacrylate Copolymer
 Ammonio Methacrylate Copolymer
 Ammonio Methacrylate Copolymer Dispersion
 Carbomer Copolymer
 Carbomer Homopolymer
 Carbomer Interpolymer
 Carboxymethylcellulose Sodium
 Cellulose, Microcrystalline
 Cellulose, Silicified Microcrystalline
 Coconut Oil, Hydrogenated
 Copovidone
 Corn Syrup
 Corn Syrup Solids
 Dextrin
 Ethyl Acrylate and Methyl Methacrylate Copolymer
 Dispersion
 Ethylcellulose
 Ethylene Glycol and Vinyl Alcohol Graft Copolymer
 Gelatin
 Glucose, Liquid
 Guar Gum
 Hydroxypropyl Cellulose, Low-Substituted
 Hydroxypropyl Methylcellulose (see Hypromellose)
 Hypromellose (formerly Hydroxypropyl Methylcellulose)
 Hypromellose Acetate Succinate
 Alpha-Lactalbumin
 Maltodextrin
 Maltose
 Methylcellulose
 Palm Oil, Hydrogenated
 Polydextrose, Hydrogenated
 Polyethylene Oxide
 Polyvinyl Acetate
 Povidone
 Pullulan
 Starch, Corn
 Starch, Hydroxypropyl Corn
 Starch, Pregelatinized Hydroxypropyl Corn
 Starch, Pea
 Starch, Hydroxypropyl Pea
 Starch, Pregelatinized Hydroxypropyl Pea

Starch, Potato
 Starch, Hydroxypropyl Potato
 Starch, Pregelatinized Hydroxypropyl Potato
 Starch, Pregelatinized
 Starch, Pregelatinized Modified
 Starch, Tapioca
 Starch, Wheat
 Starch Hydrolysate, Hydrogenated
 Syrup
 Trehalose

Tablet and/or Capsule Diluent

Calcium Carbonate
 Calcium Phosphate, Dibasic
 Calcium Phosphate, Tribasic
 Calcium Sulfate
 Cellulose, Microcrystalline
 Cellulose, Silicified Microcrystalline
 Cellulose, Powdered
 Corn Syrup
 Corn Syrup Solids
 Dextrates
 Dextrin
 Dextrose Excipient
 Fructose
 Kaolin
 Alpha-Lactalbumin
 Lactitol
 Lactose, Anhydrous
 Lactose, Monohydrate
 Maltitol
 Maltodextrin
 Maltose
 Mannitol
 Propylene Glycol Monocaprylate
 Pullulan
 Sorbitol
 Starch
 Starch, Corn
 Starch, Hydroxypropyl Corn
 Starch, Pregelatinized Hydroxypropyl Corn
 Starch, Pea
 Starch, Hydroxypropyl Pea
 Starch, Pregelatinized Hydroxypropyl Pea
 Starch, Potato
 Starch, Hydroxypropyl Potato
 Starch, Pregelatinized Hydroxypropyl Potato
 Starch, Pregelatinized
 Starch, Pregelatinized Modified
 Starch, Tapioca
 Starch, Wheat
 Starch Hydrolysate, Hydrogenated
 Sucrose
 Sugar, Compressible
 Sugar, Confectioner's
 Trehalose

Change to read:**Tablet and/or Capsule Lubricant**

Behenoyl Polyoxylglycerides
 Calcium Stearate
 Coconut Oil, Hydrogenated
 Glyceryl Behenate
 ▲Glyceryl Tristearate▲^{NF31}
 Magnesium Stearate
 Mineral Oil, Light
 Palm Oil, Hydrogenated
 Polyethylene Glycol
 Polyoxyl 10 Oleyl Ether
 Polyoxyl 15 Hydroxystearate
 Polyoxyl 20 Cetostearyl Ether
 Polyoxyl 35 Castor Oil
 Polyoxyl 40 Hydrogenated Castor Oil
 Polyoxyl 40 Stearate

Polysorbate 20
 Polysorbate 40
 Polysorbate 60
 Polysorbate 80
 Sodium Lauryl Sulfate
 Sodium Stearyl Fumarate
 Sorbitan Monolaurate
 Sorbitan Monooleate
 Sorbitan Monopalmitate
 Sorbitan Monostearate
 Sorbitan Sesquioleate
 Sorbitan Trioleate
 Starch
 Stearic Acid
 Stearic Acid, Purified
 Sucrose Stearate
 Talc
 Vegetable Oil, Hydrogenated, Type I
 Zinc Stearate

Tablet Disintegrant

Alginic Acid
 Cellulose, Microcrystalline
 Cellulose, Silicified Microcrystalline
 Croscarmellose Sodium
 Crospovidone
 Hydroxypropyl Cellulose, Low-Substituted
 Maltose
 Polacrillin Potassium
 Pullulan
 Sodium Starch Glycolate
 Starch
 Starch, Corn
 Starch, Hydroxypropyl Corn
 Starch, Pregelatinized Hydroxypropyl Corn
 Starch, Pea
 Starch, Hydroxypropyl Pea
 Starch, Pregelatinized Hydroxypropyl Pea
 Starch, Potato
 Starch, Hydroxypropyl Potato
 Starch, Pregelatinized Hydroxypropyl Potato
 Starch, Pregelatinized
 Starch, Pregelatinized Modified
 Starch, Tapioca
 Starch, Wheat
 Trehalose

Tonicity Agent

Corn Syrup
 Corn Syrup Solids
 Dextrose
 Glycerin
 Mannitol
 Potassium Chloride
 Sodium Chloride

Vehicle**FLAVORED AND/OR SWEETENED**

Aromatic Elixir
 Benzaldehyde Elixir, Compound
 Corn Syrup Solids
 Dextrose
 Ethyl Maltol
 Peppermint Water
 Sorbitol Solution
 Syrup
 Trehalose

OLEAGINOUS

Alkyl (C12-15) Benzoate
 Almond Oil
 Canola Oil

Corn Oil
 Cottonseed Oil
 Ethyl Oleate
 Isopropyl Myristate
 Isopropyl Palmitate
 Mineral Oil
 Mineral Oil, Light
 Octyldodecanol
 Olive Oil
 Peanut Oil
 Polydecene, Hydrogenated
 Polyoxyl 15 Hydroxystearate
 Safflower Oil
 Sesame Oil
 Soybean Oil
 Squalane

SOLID CARRIER

Chitosan
 Corn Syrup Solids
 Alpha-Lactalbumin
 Propylene Glycol Dicaprylate/Dicaprate
 Propylene Glycol Monocaprylate
 Sugar Spheres

STERILE

rAlbumin Human
 Sodium Chloride Injection, Bacteriostatic
 Water for Injection, Bacteriostatic

Viscosity-Increasing Agent (See *Suspending and/or Viscosity-Increasing Agent*)

Water-Repelling Agent

Cyclomethicone
 Dimethicone
 Simethicone

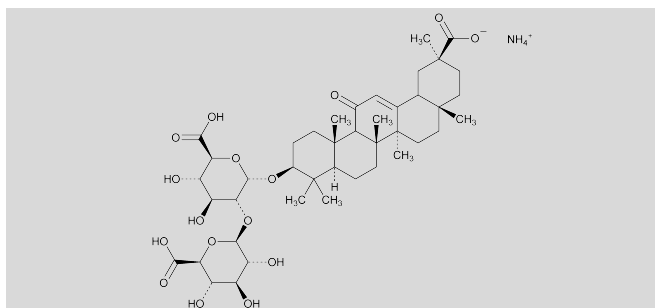
Change to read:**Wetting and/or Solubilizing Agent**

■Ammonium Glycyrrhizate ■1S (NF31)
 Benzalkonium Chloride
 Benzethonium Chloride
 Betadex Sulfobutyl Ether Sodium
 Cetylpyridinium Chloride
 Docusate Sodium
 Nonoxynol 9
 Octoxynol 9
 Poloxamer
 Polyoxyl 10 Oleyl Ether
 Polyoxyl 15 Hydroxystearate
 Polyoxyl 20 Cetostearyl Ether
 Polyoxyl 35 Castor Oil
 Polyoxyl 40 Hydrogenated Castor Oil
 Polyoxyl 40 Stearate
 Polyoxyl Stearate
 Polysorbate 20
 Polysorbate 40
 Polysorbate 60
 Polysorbate 80
 ■Propanediol ■1S (NF31)
 Pullulan
 Sodium Lauryl Sulfate
 Sorbitan Monolaurate
 Sorbitan Monooleate
 Sorbitan Monopalmitate
 Sorbitan Monostearate
 Sorbitan Sesquioleate
 Sorbitan Trioleate
 Tyloxapol

Official Monographs for NF 31

Add the following:

Ammonium Glycyrrhizate



$C_{42}H_{62}O_{16} \cdot NH_3$ 840.08
Monoammonium glycyrrhizinate;
Glycyrrhizic acid ammonium salt;
 α -D-Glucopyranosiduronic acid, (3 β ,20 β)-20-carboxy-11-oxo-30-norolean-12-en-3-yl 2-O- β -D-glucopyranuronosyl-, ammonium salt (1:1);
 α -D-Glucopyranosiduronic acid, (3 β ,20 β)-20-carboxy-11-oxo-30-norolean-12-en-3-yl 2-O- β -D-glucopyranuronosyl-, monoammonium salt [53956-04-0].

DEFINITION

Ammonium Glycyrrhizate is a mixture of ammonium 18 α - and 18 β -glycyrrhizate (ammonium salt of (20 β)-3 β -[[2-O-(β -D-glucopyranosyluronic acid)- α -D-glucopyranosyluronic acid]oxy]-11-oxoolean-12-en-29-oic acid), and the 18 β -isomer is the main component. It contains NLT 78.0% and NMT 102.0% of ammonium 18 α - and 18 β -glycyrrhizate, on the anhydrous basis.

IDENTIFICATION

- A.** The retention times of the peaks of 18 α - and 18 β -glycyrrhizic acid from the *Sample solution* correspond to those from the *System suitability solution*, as obtained in the *Content of Ammonium 18 α - and 18 β -Glycyrrhizate*.
[NOTE—The peak of 18 α -glycyrrhizic acid could be absent in the *Sample solution*.]
- B. IDENTIFICATION TESTS—GENERAL, Ammonium <191>**
Acceptance criteria: Meets the requirements

ASSAY

- CONTENT OF AMMONIUM 18 α - AND 18 β -GLYCYRRHIZATE**
Mobile phase: Acetonitrile, glacial acetic acid, and water (38:1:61)
Standard solution: 0.5 mg/mL of USP Glycyrrhizic Acid RS in *Mobile phase*
System suitability solution: 0.5 mg/mL of USP Ammonium Glycyrrhizate RS in *Mobile phase*
Sample solution: 0.5 mg/mL of Ammonium Glycyrrhizate in *Mobile phase*
Chromatographic system
(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm \times 30-cm analytical column; 5–10 μ m packing L1

Flow rate: 2.0 mL/min

Injection volume: 10 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times of 18 β -glycyrrhizic acid and 18 α -glycyrrhizic acid are about 1.0 and 1.2, respectively, *System suitability solution*.]

Suitability requirements

Resolution: NLT 2.0 between the peaks due to 18 β -glycyrrhizic acid and 18 α -glycyrrhizic acid, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution*, *System suitability solution*, and *Sample solution*

Determine the peak areas for each isomer (18 α -glycyrrhizic acid or 18 β -glycyrrhizic acid).

Calculate the percentage of ammonium 18 α -glycyrrhizate (or ammonium 18 β -glycyrrhizate) in the portion of Ammonium Glycyrrhizate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{W(\text{Salt})}/M_{W(\text{Acid})}) \times 100$$

r_U = peak area of the 18 α -glycyrrhizic acid (or 18 β -glycyrrhizic acid) in the *Sample solution*

r_S = peak area of the 18 β -glycyrrhizic acid in the *Standard solution*

C_S = concentration of the USP Glycyrrhizic Acid RS in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

$M_{W(\text{Salt})}$ = molecular weight of ammonium glycyrrhizate, 840.08 g/mol

$M_{W(\text{Acid})}$ = molecular weight of glycyrrhizic acid, 821.59 g/mol

Acceptance criteria: The total percentage of ammonium 18 α -glycyrrhizate and ammonium 18 β -glycyrrhizate is 78.0%–102.0%, and the percentage of ammonium 18 α -glycyrrhizate is NMT 13.0%, on the anhydrous basis.

IMPURITIES

RESIDUE ON IGNITION <281>

Sample: 1.0 g

Acceptance criteria: NMT 0.5%

LIMIT OF ORGANIC IMPURITIES

Mobile phase, System suitability solution, and Chromatographic system: Proceed as directed in *Content of Ammonium 18 α - and 18 β -Glycyrrhizate*.

Sample solution: 1.0 mg/mL of Ammonium Glycyrrhizate in the *Mobile phase*

Reference solution A: 0.05 mg/mL of Ammonium Glycyrrhizate in the *Mobile phase*, prepared from the *Sample solution*

Reference solution B: 0.057 mg/mL of Ammonium Glycyrrhizate in the *Mobile phase*, prepared from the *Sample solution*

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for 24-hydroxyglycyrrhizic acid, 18β-glycyrrhizic acid, and 18α-glycyrrhizic acid are about 0.7, 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the peaks due to 18β-glycyrrhizic acid and 18α-glycyrrhizic acid

Analysis

Samples: *System suitability solution, Reference solution A, Reference solution B, and Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria
24-Hydroxyglycyrrhizic acid ^a	0.7	NMT the sum of the areas of the peaks in the chromatogram from <i>Reference solution B</i> , corresponding to NMT 5.7%
Any other impurity	—	For each impurity, NMT 0.4 times the sum of the areas of the peaks in the chromatogram from <i>Reference solution A</i> , corresponding to NMT 2.0%
Sum of other impurities	—	NMT 1.6 times the sum of the areas of the peaks in the chromatogram from <i>Reference solution A</i> , corresponding to NMT 8.0%
Disregard limit	—	0.04 times the sum of the areas of the peaks in the chromatogram from <i>Reference solution A</i> , corresponding to 0.2%

^a (4β,20β)-3β-[[2-O-(β-D-Glucopyranosyluronic acid)-α-D-glucopyranosyluronic acid]oxy]-23-hydroxy-11-oxoolean-12-en-29-oic acid.

SPECIFIC TESTS

• **OPTICAL ROTATION, *Specific Rotation* (781)**

Sample solution: 10.0 mg/mL of Ammonium Glycyrrhizate in 50% ethanol

Acceptance criteria: +49.0 to +55.0 on the anhydrous basis

• **WATER DETERMINATION, *Method Ia* (921)**

Sample: 0.25 g

Acceptance criteria: NMT 6.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, and store in a cool, dry place.

• **USP REFERENCE STANDARDS (11)**

USP Ammonium Glycyrrhizate RS

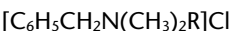
USP Glycyrrhizic Acid RS₁₅ (NF31)

Benzalkonium Chloride

Ammonium, alkyltrimethyl(phenylmethyl)-, chloride; Alkylbenzyltrimethylammonium chloride [8001-54-5].

DEFINITION

Benzalkonium Chloride is a mixture of alkylbenzyltrimethylammonium chlorides of the general formula:



in which R represents a mixture of alkyls, including all or some of the group beginning with *n*-C₈H₁₇ and extending through higher homologs, with *n*-C₁₂H₂₅, *n*-C₁₄H₂₉, and *n*-C₁₆H₃₃ composing the major portion. On the anhydrous basis, the content of the *n*-C₁₂H₂₅ homolog is NLT 40.0%, and the content of the *n*-C₁₄H₂₉ homolog is NLT 20.0% of the total alkylbenzyltrimethylammonium chloride content. The amount of the *n*-C₁₂H₂₅ and *n*-C₁₄H₂₉ homolog components together is NLT 70.0% of the total alkylbenzyltrimethylammonium chloride content. The total alkylbenzyltrimethylammonium chloride content, calculated on the anhydrous basis, with allowance made for the amount of residue on ignition, is NLT 97.0% and NMT 103.0% of [C₆H₅CH₂N(CH₃)₂R]Cl.

IDENTIFICATION

• **A.**

Analysis: To 2 mL of a solution (1 in 100) add 1 mL of 2 N nitric acid.

Acceptance criteria: A white precipitate is formed and is dissolved after adding 5 mL of alcohol.

• **B.**

Analysis: Dissolve 200 mg in 1 mL of sulfuric acid, add 100 mg of sodium nitrate, and heat on a steam bath for 5 min. Cool, dilute with water to 10 mL, add 500 mg of zinc dust, and warm for 5 min on a steam bath. To 2 mL of the clear supernatant, add 1 mL of sodium nitrite solution (1 in 20), cool in ice water, and then add 3 mL of a solution of 500 mg of 2-naphthol in 10 mL of 6 N ammonium hydroxide.

Acceptance criteria: An orange-red color is produced.

• **C. IDENTIFICATION TESTS—GENERAL, *Chloride* (191):** The solution in a mixture of equal volumes of water and alcohol meets the requirements.

• **D.** The retention times of the major peaks for benzalkonium chloride of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the test for *Ratio of Alkyl Components*.

ASSAY

• **RATIO OF ALKYL COMPONENTS**

Solution A: Adjust a 0.1 M solution of sodium acetate with glacial acetic acid to a pH of 5.0.

Mobile phase: Acetonitrile and *Solution A* (9:11). Acetonitrile and *Solution A* may be adjusted from (2:3) to (3:2) to meet system suitability requirements.

Standard solution: 4 mg/mL of benzalkonium chloride from USP Benzalkonium Chloride RS and water

Sample solution: 4 mg/mL of Benzalkonium Chloride

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; packing L10, or 4.6-mm × 25-cm; 10-μm packing L10

Flow rate: 2 mL/min

Injection volume: 20 μL

System suitability

Sample: *Standard solution*

[NOTE—See *Table 1*. Relative retention times are provided for information only, and the Standard should be used to ensure appropriate peak identification.]

Table 1

Name	Relative Retention Time
C ₁₀ homolog	0.9
C ₁₂ homolog	1.0
C ₁₄ homolog	1.3
C ₁₆ homolog	1.7

Suitability requirements**Resolution:** NLT 1.5 between the C₁₂ and C₁₄ homologs**Relative standard deviation:** NMT 2.0% for the C₁₂ homolog**Analysis****Samples:** *Standard solution* and *Sample solution*Identify the homolog peaks by comparison of the retention times of the *Sample solution* with those of the *Standard solution*.

Calculate the percentage of each quaternary ammonium homolog in the portion of Benzalkonium Chloride taken:

$$\text{Result} = \frac{r_i \times M_r}{\sum_i (r_i \times M_r)} \times 100$$

 r_U = peak area of each homolog from the *Sample solution* M_r = molecular weight of each homolog. The molecular weights of C₁₀, C₁₂, C₁₄, and C₁₆ homologs are 312, 340, 368, and 396, respectively.**Acceptance criteria:** On the anhydrous basis, the content of the *n*-C₁₂H₂₅ homolog is NLT 40.0% and the content of the *n*-C₁₄H₂₉ homolog is NLT 20.0% of the total alkylbenzyltrimethylammonium chloride content. The amount of the *n*-C₁₂H₂₅ and *n*-C₁₄H₂₉ homolog components together is NLT 70.0% of the total alkylbenzyltrimethylammonium chloride content.**Change to read:****• TOTAL ALKYL-BENZYL-DIMETHYLAMMONIUM CHLORIDES****Sample:** Weigh a quantity of Benzalkonium Chloride equivalent to 500 mg of anhydrous benzalkonium chloride.

Analysis: Transfer the *Sample*, with the aid of 35 mL of water, to a glass-stoppered, 250-mL conical separator containing 25 mL of methylene chloride. Add 10 mL of 0.1 N sodium hydroxide, and 10.0 mL of freshly prepared potassium iodide solution (1 in 20). Insert the stopper into the separator, shake, allow the layers to separate, and discard the methylene chloride layer. Wash the aqueous layer with three 10-mL portions of methylene chloride, and discard the washings. Transfer the aqueous layer to a glass-stoppered, 250-mL conical flask, and rinse the separator with three 5-mL portions of water, adding the washings to the flask. Add 40 mL of cold hydrochloric acid to the flask, mix, and titrate with 0.05 M potassium iodate VS until the solution becomes light brown in color. Add 5 mL of methylene chloride, insert the stopper into the flask, and shake vigorously. Continue the titration, dropwise, with shaking after each addition, until the methylene chloride layer no longer changes color. (IRA 1-Sep-2012) and the aqueous layer is clear yellow. Record the titrant volume, V_t , in mL. Perform a blank determination, using 20 mL of water as the sample, and record the titrant volume, V_b , in mL. [NOTE— $V_b > V_t$.] The difference between the two titrations represents the amount of potassium iodate equivalent to the weight of benzalkonium chloride in the sample. Each mL of 0.05 M potassium iodate is equivalent to $x/10$ mg of benzalkonium chloride, where x represents the average molecular weight of the sample, derived by summing, for all homologs, the products:

$$\text{Result } (x) = \sum_i [(r_U/r_T) \times M_r]$$

 r_U = peak area of each homolog from the *Ratio of Alkyl Components* test r_T = sum of all the peak areas of the homologs from the *Ratio of Alkyl Components* test M_r = molecular weight of each homolog. The molecular weights of the C₁₀, C₁₂, C₁₄, and C₁₆ homologs are 312, 340, 368, and 396, respectively.**Acceptance criteria:** 97.0%–103.0% on the anhydrous basis**IMPURITIES****• RESIDUE ON IGNITION (281):** NMT 2.0%**• LIMIT OF AMINES AND AMINE SALTS****Sample:** 5.0 g of Benzalkonium Chloride**Analysis:** Dissolve the *Sample* by heating carefully (e.g., on top of a steam bath with water as the steam source) in 20 mL of a mixture of methanol and 1 N hydrochloric acid VS (97:3). [NOTE—The mixed solution, however, must not reach the boiling point.] Add 100 mL of isopropyl alcohol, and pass a stream of nitrogen slowly through the solution. Gradually add 12.0 mL of 0.1 N tetrabutylammonium hydroxide VS while recording the potentiometric titration curve.**Acceptance criteria:** If the curve shows two inflection points, the volume of titrant added between the two points is NMT 5.0 mL, corresponding to NMT 0.1 mmol/g of amines and amine salts. If the curve shows no point of inflection, the substance being examined does not comply with the test. If the curve shows one point of inflection, repeat the test, but add 3.0 mL of a 25.0 mg/mL solution of dimethyldodecylamine in isopropyl alcohol before the titration. If after addition of 12.0 mL of the titrant, the titration curve shows only one point of inflection, the substance being examined does not comply with the test.**• LIMIT OF BENZYL ALCOHOL, BENZALDEHYDE, AND (CHLOROMETHYL)BENZENE**

[NOTE—Prepare the solutions immediately before use.]

Solution A: Dissolve 1.09 g of sodium 1-hexanesulfonate and 6.9 g of monobasic sodium phosphate in water in a 1000-mL volumetric flask, adjust with phosphoric acid to a pH of 3.5, and dilute with water to volume.**Solution B:** Methanol**Mobile phase:** See Table 2.**Table 2**

Time (min)	Solution A (%)	Solution B (%)
0	80	20
10	80	20
14	50	50
35	50	50
36	20	80
55	20	80
56	80	20
65	80	20

Standard solution A: 0.25 mg/mL of USP Benzyl Alcohol RS in methanol**Standard solution B:** 0.075 mg/mL of USP Benzaldehyde RS in methanol**Standard solution C:** 0.025 mg/mL of USP Benzyl Alcohol RS in methanol, prepared from *Standard solution A* and methanol**Sample solution:** 50 mg/mL of Benzalkonium Chloride in methanol**Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 210 nm for benzyl alcohol and (chloromethyl)benzene; UV 257 nm for benzaldehyde

Column: 4.6-mm × 15-cm; 5-μm packing L1

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection volume: 20 μL

System suitability

Samples: Standard solution A, Standard solution B, Standard solution C, and Sample solution

[NOTE—See Table 3 for relative retention times.]

Table 3

Name	Relative Retention Time
Benzyl alcohol	1.0
Benzaldehyde	1.3
(Chloromethyl)benzene	2.4

Suitability requirements

Relative standard deviation: NMT 5.0% for benzyl alcohol, Standard solution A

Signal-to-noise ratio: NLT 10 for the principal peak, Standard solution C

Analysis

Samples: Standard solution A, Standard solution B, Standard solution C, and Sample solution

Calculate the content of (chloromethyl)benzene by multiplying the peak area of (chloromethyl)benzene by 1.3. [NOTE—The correction factor is used to adjust for baseline shift.]

Acceptance criteria

Benzyl alcohol: The response of the benzyl alcohol peak from the *Sample solution* is NMT that of the benzyl alcohol peak from *Standard solution A*, corresponding to NMT 0.5%.

Benzaldehyde: The response of the benzaldehyde peak from the *Sample solution* is NMT that of the benzaldehyde peak from *Standard solution B*, corresponding to NMT 0.15%.

(Chloromethyl)benzene: The response of the (chloromethyl)benzene peak from the *Sample solution* is NMT 0.1 times that of the principal peak from *Standard solution A*, corresponding to NMT 0.05%.

SPECIFIC TESTS

Change to read:

• ACIDITY OR ALKALINITY

Sample: 0.5 g of Benzalkonium Chloride

Analysis: Dissolve the *Sample* in water, dilute with water to 50 mL, and mix. Add 0.1 mL of bromocresol purple TS.

Acceptance criteria: NMT 0.5 mL of 0.1 N hydrochloric acid or 0.1 N sodium hydroxide is required to change the color of the indicator.

• WATER DETERMINATION, Method I (921): NMT 15.0%

• WATER-INSOLUBLE MATTER: A solution (1 in 10) is free from turbidity and insoluble matter.

ADDITIONAL REQUIREMENTS

• PACKAGING AND STORAGE: Preserve in tight containers. No storage requirements specified.

• USP REFERENCE STANDARDS (11)

USP Benzaldehyde RS
USP Benzalkonium Chloride RS
USP Benzyl Alcohol RS

Benzalkonium Chloride Solution

DEFINITION

Benzalkonium Chloride Solution contains NLT 95.0% and NMT 105.0% of the labeled amount of benzalkonium chloride in a solution having a concentration of 1.0% or more; and NLT 93.0% and NMT 107.0% of the labeled amount of benzalkonium chloride in a solution having a concentration of less than 1.0%. It may contain a suitable coloring agent and may contain NMT 10% of alcohol.

[CAUTION—Mixing Benzalkonium Chloride Solution with ordinary soaps and anionic detergents may decrease or destroy the bacteriostatic activity of the Solution.]

IDENTIFICATION

• A.

Analysis: To 2 mL of a solution having an equivalent of 10 mg/mL of benzalkonium chloride add 1 mL of 2 N nitric acid.

Acceptance criteria: A white precipitate is formed, and is dissolved after adding 5 mL of alcohol.

• B. IDENTIFICATION TESTS—GENERAL, Chloride (191): A solution of it in a mixture of equal volumes of water and alcohol meets the requirements.

• C.

Analysis: Dissolve the residue obtained by evaporating on a steam bath a volume of Solution equivalent to 200 mg of benzalkonium chloride in 1 mL of sulfuric acid. Add 100 mg of sodium nitrate, and heat on a steam bath for 5 min. Cool, dilute with water to 10 mL, add 500 mg of zinc dust, and warm for 5 min on a steam bath. To 2 mL of the clear supernatant add 1 mL of sodium nitrite solution (1 in 20), cool in ice water, then add 3 mL of a solution of 500 mg of 2-naphthol in 10 mL of 6 N ammonium hydroxide.

Acceptance criteria: An orange-red color is produced.

• D. The retention times of the major peaks for benzalkonium chloride of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the test for *Ratio of Alkyl Components*.

ASSAY

• RATIO OF ALKYL COMPONENTS

Solution A: Adjust a 0.1 M solution of sodium acetate with glacial acetic acid to a pH of 5.0.

Mobile phase: Acetonitrile and *Solution A* (9:11). Acetonitrile and *Solution A* may be adjusted from (2:3) to (3:2) to meet system suitability requirements.

Standard solution: 4 mg/mL of benzalkonium chloride, prepared from USP Benzalkonium Chloride RS and water

Sample solution: Transfer a volume of Solution, equivalent to 400 mg of benzalkonium chloride, to a 100-mL volumetric flask, and dilute with water to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 30-cm; packing L10, or 4.6-mm × 25-cm; 10-μm packing L10

Flow rate: 2 mL/min

Injection volume: 20 μL

System suitability

Sample: *Standard solution*

[NOTE—See Table 1. Relative retention times are provided for information only, and the Standard should be used to ensure appropriate peak identification.]

Table 1

Name	Relative Retention Time
C ₁₀ homolog	0.9
C ₁₂ homolog	1.0
C ₁₄ homolog	1.3
C ₁₆ homolog	1.7

Suitability requirements

Resolution: NLT 1.5 between the C₁₂ and C₁₄ homologs

Relative standard deviation: NMT 2.0% for the C₁₂ homolog

Analysis

Samples: *Standard solution* and *Sample solution*

Identify the homolog peaks by comparison of the retention times of the *Sample solution* with those of the *Standard solution*.

Calculate the percentage of each quaternary ammonium homolog in the portion of Solution taken:

$$\text{Result} = \frac{r_U \times M_r}{\sum (r_U \times M_r)} \times 100$$

r_U = peak area of each homolog from the *Sample solution*

M_r = molecular weight of each homolog. The molecular weights of the C₁₀, C₁₂, C₁₄, and C₁₆ homologs are 312, 340, 368, and 396, respectively.

Acceptance criteria: On the solid basis, the content of the *n*-C₁₂H₂₅ homolog is NLT 40.0%, and the content of the *n*-C₁₄H₂₉ homolog is NLT 20.0% of the total alkylbenzyltrimethylammonium chloride content. The amount of the *n*-C₁₂H₂₅ and *n*-C₁₄H₂₉ homolog components together is NLT 70.0% of the total alkylbenzyltrimethylammonium chloride content.

Change to read:**• TOTAL ALKYL BENZYL DIMETHYLAMMONIUM CHLORIDES**

Sample solution: Evaporate or dilute with water to 30 mL a volume of Solution equivalent to 500 mg of benzalkonium chloride.

Analysis: Transfer the *Sample solution*, with the aid of a minimum quantity of water, to a glass-stoppered, 250-mL conical separator. Transfer 25 mL of methylene chloride. Add 10 mL of 0.1 N sodium hydroxide, and 10.0 mL of freshly prepared potassium iodide solution (1 in 20), insert the stopper in the separator, shake, allow the layers to separate, and discard the methylene chloride layer. Wash the aqueous layer with three 10-mL portions of methylene chloride, and discard the washings. Transfer the aqueous layer to a glass-stoppered, 250-mL conical flask, and rinse the separator with three 5-mL portions of water, adding the washings to the flask. Add 40 mL of cold hydrochloric acid to the flask, mix, and titrate with 0.05 M potassium iodate VS until the solution becomes light brown in color. Add 5 mL of methylene chloride, insert the stopper into the flask, and shake vigorously. Continue the titration, dropwise, with shaking after each addition, until the methylene chloride layer **no longer changes color.** (IRA

1-Sep-2012) and the aqueous layer is clear yellow. Record the titrant volume, V_t , in mL. Perform a blank determination, using 20 mL of water as the sample, and record the titrant volume, V_b , in mL. [NOTE— $V_b > V_t$.] The difference between the two titrations represents the

amount of potassium iodate equivalent to the weight of benzalkonium chloride in the sample. Each mL of 0.05 M potassium iodate is equivalent to $x/10$ mg of benzalkonium chloride, where x represents the average molecular weight of the sample, derived by summing, for all homologs, the products:

$$\text{Result } (x) = \sum [(r_U/r_T) \times M_r]$$

r_U = peak area of each homolog from the *Ratio of Alkyl Components* test

r_T = sum of all the peak areas of the homologs from the *Ratio of Alkyl Components* test

M_r = molecular weight of each homolog. The molecular weights of the C₁₀, C₁₂, C₁₄, and C₁₆ homologs are 312, 340, 368, and 396, respectively.

Acceptance criteria

For labeled concentrations of NLT 1.0%:

95.0%–105.0%

For labeled concentrations less than 1.0%:

93.0%–107.0%

OTHER COMPONENTS**Change to read:****• ALCOHOL CONTENT (if added)**

Internal standard solution: 0.06 mL/mL of tertiary butyl alcohol in water

Alcohol stock solution: •0.015 mL/mL of alcohol (C₂H₅OH) in water, from USP Alcohol Determination—Alcohol RS. (IRA 1-Sep-2012)

Standard solutions: Introduce •10, 20, and 40 mL, • (IRA 1-Sep-2012) respectively, of *Alcohol stock solution* into three separate identical 50-mL volumetric flasks. To each flask add a 5-mL portion of the *Internal standard solution*. Dilute with water to volume, and mix thoroughly. The *Standard solutions* contain 0.003, 0.006, and 0.012 mL/mL of alcohol (C₂H₅OH), respectively.

Sample solution: Weigh an appropriate amount of Solution into a 50-mL volumetric flask, and pipet 5 mL of the *Internal standard solution* into the flask. Dilute with water to volume, and mix thoroughly to obtain a solution containing 0.003–0.012 mL/mL of alcohol (C₂H₅OH).

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.25-mm × 30-m glass or quartz capillary; 1.4-μm layer of phase G43

Temperatures

Detector: 250°

Injection port: 250°

Column: See Table 2.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	—	40	7
40	30	250	15

Run time: 29 min

Carrier gas: Helium or nitrogen

Flow rate: See Table 3.

Table 3

Initial Flow (mL/min)	Flow Ramp (mL/min ²)	Final Flow (mL/min)	Hold Time at Final Flow (min)
1	—	1	8
1	10	3	21

Injection volume: 1 μ L

Injection type: Split 75:1

System suitability

Sample: *Standard solution* containing 0.006 mL/mL of alcohol (C₂H₅OH)

[NOTE—The relative retention times for alcohol and tertiary butyl alcohol are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between alcohol and tertiary butyl alcohol

Relative standard deviation: NMT 10%

Analysis

Samples: *Standard solutions* and *Sample solution*

Plot the peak response ratios of the alcohol to tertiary butyl alcohol in the *Standard solutions* versus the content, in mL/mL, of alcohol, and draw the straight line best fitting the plotted points. From the graph obtained, determine the content, *C*, in mL/mL, of alcohol (C₂H₅OH) in the *Sample solution*.

Calculate the percentage of alcohol (C₂H₅OH) in the portion of Solution (v/v) taken:

$$\text{Result} = V \times (C \times D/W) \times 100$$

V = volume of the *Sample solution*, 50 mL

D = density of Benzalkonium Chloride Solution (g/mL)

W = weight of Benzalkonium Chloride Solution taken to prepare the *Sample solution* (g)

Acceptance criteria: If present, 95.0%–105.0% of the labeled amount of alcohol (C₂H₅OH)

IMPURITIES

• LIMIT OF AMINES AND AMINE SALTS

Sample: A quantity of Solution equivalent to 5.0 g of benzalkonium chloride

Analysis: Dissolve the *Sample* by heating carefully (e.g., on top of a steam bath with water as the steam source) in 20 mL of a mixture of methanol and 1 N hydrochloric acid VS (97:3). [NOTE—The mixed solution, however, must not reach the boiling point.] Add 100 mL of isopropyl alcohol, and pass a stream of nitrogen slowly through the solution. Gradually add 12.0 mL of 0.1 N tetrabutylammonium hydroxide VS while recording the potentiometric titration curve.

Acceptance criteria: If the curve shows two inflection points, the volume of titrant added between the two points is NMT 5.0 mL, corresponding to NMT 0.1 mmol/g of amines and amine salts. If the curve shows no point of inflection, the substance being examined does not comply with the test. If the curve shows one point of inflection, repeat the test, but add 3.0 mL of a 25.0 mg/mL solution of dimethyldecylamine in isopropyl alcohol before the titration. If after the addition of 12.0 mL of the titrant, the titration curve shows only one point of inflection, the substance being examined does not comply with the test.

• LIMIT OF BENZYL ALCOHOL, BENZALDEHYDE, AND (CHLOROMETHYL)BENZENE

[NOTE—Prepare the solutions immediately before use.]

Solution A: Dissolve 1.09 g of sodium 1-hexanesulfonate and 6.9 g of monobasic sodium phosphate in water in a 1000-mL volumetric flask, adjust with phosphoric acid to a pH of 3.5, and dilute with water to volume.

Solution B: Methanol

Mobile phase: See Table 4.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	80	20
10	80	20
14	50	50
35	50	50
36	20	80
55	20	80
56	80	20
65	80	20

Standard solution A: 0.25 mg/mL of USP Benzyl Alcohol RS in methanol

Standard solution B: 0.075 mg/mL of USP Benzaldehyde RS in methanol

Standard solution C: 0.025 mg/mL of USP Benzyl Alcohol RS in methanol, prepared from *Standard solution A* and methanol

Sample solution: Determine the density of the Solution. Dilute a quantity of the Solution equivalent to 2.5 g of benzalkonium chloride with methanol to 50.0 mL. This solution contains 50 mg/mL of benzalkonium chloride.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm for benzyl alcohol and (chloromethyl)benzene; UV 257 nm for benzaldehyde

Column: 4.6-mm \times 15-cm; 5- μ m packing L1

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection volume: 20 μ L

System suitability

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, and *Sample solution*

[NOTE—See Table 5 for relative retention times.]

Table 5

Name	Relative Retention Time
Benzyl alcohol	1.0
Benzaldehyde	1.3
(Chloromethyl)benzene	2.4

Suitability requirements

Relative standard deviation: NMT 5.0% for benzyl alcohol, *Standard solution A*

Signal-to-noise ratio: NLT 10 for the principal peak, *Standard solution C*

Analysis

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, and *Sample solution*

Calculate the content of (chloromethyl)benzene by multiplying the peak area of (chloromethyl)benzene by 1.3. [NOTE—The correction factor is used to adjust for baseline shift.]

Acceptance criteria

Benzyl alcohol: The response of the benzyl alcohol peak from the *Sample solution* is NMT that of the benzyl alcohol peak from *Standard solution A*, corresponding to NMT 0.5%.

Benzaldehyde: The response of the benzaldehyde peak from the *Sample solution* is NMT that of the benzaldehyde peak from *Standard solution B*, corresponding to NMT 0.15%.

(Chloromethyl)benzene: The response of the (chloromethyl)benzene peak from the *Sample solution*

is NMT 0.1 times that of the principal peak from *Standard solution A*, corresponding to NMT 0.05%.

SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): A solution containing less than 5.0% of benzalkonium chloride meets the requirements of the test for absence of *Pseudomonas aeruginosa*.

Change to read:

• ACIDITY OR ALKALINITY

Sample solution: Evaporate or dilute with carbon dioxide-free water to prepare a 50-mL solution of 10 mg/mL of benzalkonium chloride in water. (IRA 1-Sep-2012)

Analysis: To the *Sample solution* add 0.1 mL of bromocresol purple TS.

Acceptance criteria: NMT 0.5 mL of 0.1 N hydrochloric acid or 0.1 N sodium hydroxide is required to change the color of the indicator.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and prevent contact with metals.
- **LABELING:** Label it to indicate the concentration of benzalkonium chloride, and to indicate the name and quantity of the coloring agent added. The labeling also indicates the concentration of alcohol added.

Change to read:

• USP REFERENCE STANDARDS (11)

- USP Alcohol Determination—Alcohol RS. (IRA 1-Sep-2012)
- USP Benzaldehyde RS
- USP Benzalkonium Chloride RS
- USP Benzyl Alcohol RS

Butane

C₄H₁₀ 58.12
n-Butane [106-97-8].

DEFINITION

Butane contains NLT 97.0% of butane (C₄H₁₀).
[CAUTION—Butane is highly flammable and explosive.]

IDENTIFICATION

- **A. INFRARED ABSORPTION:** Exhibits maxima, among others, at the following wavelengths, in μm: 3.4 (vs), 6.8 (s), 7.2 (m), and 10.4 (m)
- **B. Sample:** Use an empty stainless steel cylinder equipped with a stainless steel valve, having a capacity of NLT 200 mL, and a pressure rating of 240 psi or more. Dry the cylinder with the valve open at 110° for 2 h, and evacuate the hot cylinder to less than 1 mm of mercury. Close the valve, cool, and weigh. Connect one end of a charging line tightly to the butane container and the other end loosely to the empty cylinder. Carefully open the butane container, and allow the butane to flush out the charging line through the loose connection. Avoid excessive flushing, which causes moisture to freeze in the charging line and connections. Tighten the fitting on the empty cylinder, and open the empty cylinder valve, allowing the butane to flow into the evacuated cylinder. Continue sampling until the desired amount of butane is obtained, then close the butane container valve, and finally close the sample cylinder valve. **[CAUTION—**Do not overload the sample cylinder; hydraulic expansion due to temperature change can cause over-

loaded cylinders to explode.] Weigh the charged sample cylinder, and determine the weight.

Analysis: Determine the vapor pressure of the *Sample* at 21° by means of a suitable pressure gauge.

Acceptance criteria: 205–235 kPa absolute (30–34 psia)

ASSAY

Change to read:

• PROCEDURE

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: GC

Detector: Thermal conductivity

Column: 3-mm × 6-m aluminum; packed with 10 weight percent of liquid phase G30 on support S1D1S (NF31)

Column temperature: 33°

Carrier gas: Helium

Flow rate: 50 mL/min

Injection volume: 2 μL

System suitability

Sample: *n*-Butane

Suitability requirements: The peak responses of *n*-butane in the chromatograms from duplicate determinations agree within 1%.

Analysis

Samples: Connect one Butane cylinder to the chromatograph through a suitable sampling valve and a flow control valve downstream from the sampling valve. Flush the liquid specimen through the sampling valve, taking care to avoid entrapment of gas or air in the sampling valve.

Calculate the purity by dividing 100 times the *n*-butane response by the sum of all of the responses.

Acceptance criteria: NLT 97.0%

SPECIFIC TESTS

• HIGH-BOILING RESIDUES

Sample: Use the *Sample* from *Identification* test B.

Analysis: Prepare a cooling coil from copper tubing (about 6-mm outside diameter × about 6.1-m long) to fit into a vacuum-jacketed flask. Immerse the cooling coil in a mixture of dry ice and acetone in a vacuum-jacketed flask, and connect one end of the tubing to the *Sample*. Carefully open the sample cylinder valve, flush the cooling coil with about 50 mL of the *Sample*, and discard this portion of liquefied sample. Continue delivering liquefied sample from the cooling coil, and collect it in a previously chilled 1000-mL sedimentation cone until the cone is filled to the 1000-mL mark. Allow the sample to evaporate, using a warm water bath maintained at about 40° to reduce evaporating time. When all of the liquid has evaporated, rinse the sedimentation cone with two 50-mL portions of pentane, and combine the rinsings in a tared 150-mL evaporating dish. Transfer 100 mL of the pentane solvent to a second tared 150-mL evaporating dish, place both evaporating dishes on a water bath, evaporate to dryness, and heat the dishes in an oven at 100° for 60 min. Cool the dishes in a desiccator, and weigh. Repeat the heating for 15-min periods until successive weighings are within 0.1 mg, and calculate the weight of the residue obtained from the *Sample* as the difference between the weights of the residues in the two evaporating dishes.

Acceptance criteria: NMT 5 μg/mL

• ACIDITY OF RESIDUE

Sample solution: Add 10 mL of water to the residue obtained in the test for *High-Boiling Residues*.

Analysis: Mix the *Sample solution* by swirling for 30 s, add 2 drops of methyl orange TS, insert the stopper in the tube, and shake vigorously.

Acceptance criteria: No pink or red color appears in the aqueous layer.

• **LIMIT OF SULFUR COMPOUNDS**

Analysis: Carefully open the container valve to produce a moderate flow of gas. Do not direct the gas stream toward the face, but deflect a portion of the stream toward the nose.

Acceptance criteria: The odor is free from the characteristic odor of sulfur compounds.

• **WATER DETERMINATION (921)**

Sample: 100 g of the *Sample* from Identification test B

Analysis: Proceed as directed in the chapter with the following modifications. (a) Provide the closed-system titrating vessel with an opening through which passes a coarse-porosity gas dispersion tube connected to a sampling cylinder. (b) Dilute the *Reagent* with anhydrous methanol to give a water equivalence factor of 0.2–1.0 mg/mL; age this diluted solution for NLT 16 h before standardization. (c) Introduce the *Sample* into the titration vessel through the gas dispersion tube at a rate of about 100 mL/min; if necessary, heat the sample cylinder gently to maintain this flow rate.

Acceptance criteria: NMT 0.001%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight cylinders, and prevent exposure to excessive heat.

Add the following:

Butyl Palmitostearate



DEFINITION

Butyl Palmitostearate is a mixture of the butyl ester of stearic acid ($C_{18}H_{36}O_2$) and the butyl ester of palmitic acid ($C_{16}H_{32}O_2$). It contains 40.0%–80.0% of butyl stearate ($C_{22}H_{44}O_2$). The total percentage of butyl stearate ($C_{22}H_{44}O_2$) and butyl palmitate ($C_{20}H_{40}O_2$) is NLT 90.0%.

IDENTIFICATION

- **A.** It meets the requirements of the test for *Content of Butyl Palmitate and Butyl Stearate*.

ASSAY

• **CONTENT OF BUTYL PALMITATE AND BUTYL STEARATE**

Standard solution A: 2.0 mg/mL of USP Butyl Stearate RS in chloroform

Standard solution B: 1.0 mg/mL of USP Butyl Palmitate RS in chloroform

System suitability solution: 1.4 µg/mL of USP Butyl Stearate RS and 1.0 µg/mL of USP Butyl Palmitate RS in chloroform, prepared from *Standard solution A*, *Standard solution B*, and chloroform

Sample solution: 2.0 mg/mL of Butyl Palmitostearate in chloroform

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m capillary; bonded with a 0.25-µm layer of thickness of phase G27

Temperatures

Detector: 280°

Injection port: 280°

Column: See Table 1.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
60	—	60	2
60	4	250	20.5

Carrier gas: Helium

Flow rate: 1.4 mL/min

Injection volume: 1 µL

Injection type: Split injection, split ratio is 5:1

System suitability

Samples: *Standard solution A* and *System suitability solution*

[NOTE—The relative retention times for butyl palmitate and butyl stearate are 0.91 and 1.00, respectively.]

System suitability requirements

Resolution: NLT 20 between butyl palmitate and butyl stearate, *System suitability solution*

Tailing factor: NMT 2.0 for the butyl stearate peak, *System suitability solution*

Relative standard deviation: NMT 3.0% for the butyl stearate peak, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Identify the butyl palmitate and butyl stearate peaks in the *Sample solution* based on those in *Standard solution A* and *Standard solution B*.

Calculate the percentage of butyl palmitate or butyl stearate in the portion of Butyl Palmitostearate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of butyl palmitate or butyl stearate from the *Sample solution*

r_S = peak response of butyl palmitate from *Standard solution B* or peak response of butyl stearate from *Standard solution A*

C_S = concentration of USP Butyl Palmitate RS in *Standard solution B* or concentration of USP Butyl Stearate RS in *Standard solution A*

C_U = concentration of Butyl Palmitostearate in the *Sample solution*

Acceptance criteria

Content of butyl stearate: 40.0%–80.0%

Sum of butyl stearate and butyl palmitate: NLT 90.0%

SPECIFIC TESTS

- **MELTING RANGE OR TEMPERATURE, Class II (741):** 17°–24°

- **FATS AND FIXED OILS, Acid Value (401):** NMT 0.5

- **FATS AND FIXED OILS, Iodine Value (401):** NMT 1.0

- **FATS AND FIXED OILS, Saponification Value (401):** 165–180

- **WATER DETERMINATION, Method 1a (921):** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature. Keep away from heat and sources of ignition.

- **USP REFERENCE STANDARDS (11)**

USP Butyl Palmitate RS

USP Butyl Stearate RS₁₅ (NF31)

Add the following:**•Butyl Stearate**
 $C_{22}H_{44}O_2$ 340.59

Octadecanoic acid, butyl ester;
Butyl octadecanoate [123-95-5].

DEFINITION

Butyl Stearate consists of the esters of butyl alcohol and fatty acids composed chiefly of stearic acid ($C_{18}H_{36}O_2$) and a minor amount of palmitic acid ($C_{16}H_{32}O_2$). It contains NLT 90.0% of butyl stearate [$C_{22}H_{44}O_2$ (M_w 340.59)], and the total of butyl stearate ($C_{22}H_{44}O_2$) and butyl palmitate [$C_{20}H_{40}O_2$ (M_w 312.53)] is NLT 96.0%.

IDENTIFICATION

- A.** It meets the requirements of the test for *Content of Butyl Palmitate and Butyl Stearate*.

ASSAY**• CONTENT OF BUTYL PALMITATE AND BUTYL STEARATE**

Standard solution A: 2.0 mg/mL of USP Butyl Stearate RS in chloroform

Standard solution B: 0.2 mg/mL of USP Butyl Palmitate RS in chloroform

System suitability solution: 1.4 µg/mL of USP Butyl Stearate RS and 1.0 µg/mL of USP Butyl Palmitate RS in chloroform, prepared from *Standard solution A*, *Standard solution B*, and chloroform

Sample solution: 2.0 mg/mL of Butyl Stearate in chloroform

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.32-mm × 30-m capillary; bonded with a 0.25-µm layer of thickness of phase G27

Temperatures

Detector: 280°

Injection port: 280°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
60	—	60	2
60	4	250	20.5

Carrier gas: Helium

Flow rate: 1.4 mL/min

Injection volume: 1 µL

Injection type: Split injection, split ratio is 5:1.

System suitability

Samples: *System suitability solution* and *Standard solution A*

[NOTE—The relative retention times for butyl palmitate and butyl stearate are 0.91 and 1.00, respectively.]

System suitability requirements

Resolution: NLT 20 between butyl palmitate and butyl stearate, *System suitability solution*

Tailing factor: NMT 2.0 for the butyl stearate peak, *System suitability solution*

Relative standard deviation: NMT 3.0% for the butyl stearate peak, *Standard solution A*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Identify the butyl palmitate and butyl stearate peaks in the *Sample solution* based on those in *Standard solution A* and *Standard solution B*.

Calculate the percentage of butyl palmitate or butyl stearate in the portion of Butyl Stearate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of butyl palmitate or butyl stearate from the *Sample solution*

r_S = peak response of butyl palmitate from *Standard solution B* or peak response of butyl stearate from *Standard solution A*

C_S = concentration of USP Butyl Palmitate RS in *Standard solution B* or concentration of USP Butyl Stearate RS in *Standard solution A*

C_U = concentration of Butyl Stearate in the *Sample solution*

Acceptance criteria: NLT 90.0% of butyl stearate and NLT 96.0% for the sum of butyl stearate and butyl palmitate

SPECIFIC TESTS

• **MELTING RANGE OR TEMPERATURE**, *Class II* <741>: 19°–24°

• **FATS AND FIXED OILS**, *Acid Value* <401>: NMT 0.5

• **FATS AND FIXED OILS**, *Iodine Value* <401>: NMT 1.0

• **FATS AND FIXED OILS**, *Saponification Value* <401>: 165–180

• **WATER DETERMINATION**, *Method Ia* <921>: NMT 0.5%

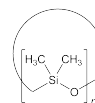
ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature. Keep away from heat and sources of ignition.

• USP REFERENCE STANDARDS <11>

USP Butyl Palmitate RS

USP Butyl Stearate RS^{1S} (NF31)

Cyclomethicone**Change to read:**

(C_2H_6OSi)_n

Cyclopolydimethylsiloxane;

■Cyclic polydimethylsiloxanes;

Cyclodimethicone^{1S} (NF31) [69430-24-6].

DEFINITION

Cyclomethicone is a fully methylated cyclic siloxane containing repeating units of $[-(CH_3)_2SiO-]_n$, in which n is 4, 5, 6, or a mixture of them. It contains NLT 98.0% of (C_2H_6OSi)_n, calculated as the sum of cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6, and NLT 95.0% and NMT 105.0% of the labeled amount of any one or more of the individual cyclomethicone components.

IDENTIFICATION**• A. INFRARED ABSORPTION <197S>**

Sample: Use neat liquids.

Acceptance criteria: The IR absorption spectrum exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cyclomethicone 4 RS, USP Cyclomethicone 5 RS, or USP Cyclomethicone 6 RS.

ASSAY

Change to read:

PROCEDURE

Standard solution A: USP Cyclomethicone 4 RS (neat)
Standard solution B: USP Cyclomethicone 5 RS (neat)
Standard solution C: USP Cyclomethicone 6 RS (neat)
Sample solution: Cyclomethicone (neat)
Chromatographic system
 (See *Chromatography* <621>, *System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 0.32-mm × 60-m fused silica; coated with a 1.0-μm film of phase G1
Temperatures
Injection port: 250°
Detector: 300°
Column: See Table 1.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
60	—	60	5
60	10	200	15
200	5	225	5

Carrier gas: Helium
Flow rate: 1 mL/min
Injection volume: 1 μL
Injection type: Split ratio 1:20
System suitability
Samples: Standard solution A, Standard solution B, and Standard solution C
 [NOTE—See Table 2.]

Table 2

Name	Relative Retention Time
Cyclomethicone 4	0.9
Cyclomethicone 5	1.0
Cyclomethicone 6	1.2

Suitability requirements

Relative standard deviation: NMT 2.0% for cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6, Standard solution A, Standard solution B, and Standard solution C

Calculate the percentage of cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6 by dividing 100 times the response of each peak at the retention time of the corresponding reference standard by the sum of all of the responses in the chromatogram. The percentages obtained from duplicate injections agree to within 1.0%.

Analysis

Samples: Standard solution A, Standard solution B, Standard solution C, and Sample solution
 Calculate the percentage of cyclomethicone 4 (cyclomethicone 5 or cyclomethicone 6) in the portion of Cyclomethicone taken:

$$\text{Result} = (r_u/r_T) \times 100$$

r_u = peak response of cyclomethicone 4 (cyclomethicone 5 or cyclomethicone 6)

r_T = sum of all the peak responses

Calculate the percentage purity by adding the percentages of cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6.

Acceptance criteria

Sum of cyclomethicone 4, cyclomethicone 5, and cyclomethicone 6: NLT 98.0% of (C₂H₆OSi)_n

Labeled amount: 95.0%–105.0% of the labeled amount of any one or more of the individual cyclomethicone components ■1S (NF31)

IMPURITIES

LIMIT OF NONVOLATILE RESIDUE

Sample: 2.0 g

Analysis: Transfer the Sample into an open, tared aluminum dish, and evaporate in a circulating air oven at 150° for 2 h. Allow to cool in a desiccator, and weigh.

Acceptance criteria: NMT 3.0 mg, corresponding to NMT 0.15% (w/w)

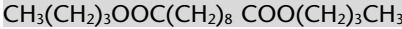
ADDITIONAL REQUIREMENTS

Change to read:

- PACKAGING AND STORAGE:** Preserve in tight containers. ■Avoid exposure to excessive heat. ■1S (NF31)
- LABELING:** Label it to state, as part of the official title, the *n*-value of the Cyclomethicone. Where it is a mixture of two or three such cyclic siloxanes, the label states the *n*-value and percentage of each in the mixture.
- USP REFERENCE STANDARDS** <11>
 USP Cyclomethicone 4 RS
 USP Cyclomethicone 5 RS
 USP Cyclomethicone 6 RS

Dibutyl Sebacate

Add the following:



Decanedioic acid, 1,10-dibutyl ester;

Dibutyl 1,10-decanedioate;

Sebacic acid di-*n*-butyl ester [109-43-3]. ■1S (NF31)

DEFINITION

Change to read:

Dibutyl Sebacate consists of esters of *n*-butyl alcohol and saturated dibasic acids, principally sebacic acid. It contains NLT 92.0% ■and NMT 102.0% ■1S (NF31) of dibutyl sebacate (C₃₁H₅₄O₄).

IDENTIFICATION**Add the following:**

- **A. INFRARED ABSORPTION** <197F>
Sample: Undried specimen
Acceptance criteria: Meets the requirements. ■1S (NF31)

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■1S (NF31)

ASSAY**Change to read:**

- **PROCEDURE**
Internal standard solution: 0.9 mg/mL of methyl heptadecanoate in alcohol
Standard solution: 1.0 mg/mL of USP Dibutyl Sebacate RS in the *Internal standard solution*
Sample solution: 1.0 mg/mL of Dibutyl Sebacate in the *Internal standard solution*
Chromatographic system
(See *Chromatography* <621>, *System Suitability*.)
Mode: GC
Detector: Flame ionization
Column: 0.32-mm × 30-m fused silica column, coated with a 0.25-μm film of phase G2
Temperature
Detector: 300°
Injection port: 300°
Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
150	—	150	5
150	10	250	5

Carrier gas: Helium

Linear velocity: 50 cm/s

Injection volume: 1 μL

Injection type: Split injection, split ratio is about 30:1

Run time: 20 min

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for dibutyl sebacate and methyl heptadecanoate are 1.0 and 0.9, respectively.]

Suitability requirements

Resolution: NLT 2.0 between methyl heptadecanoate and dibutyl sebacate

Relative standard deviation: NMT 2.0% for the peak response ratio of dibutyl sebacate to methyl heptadecanoate

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dibutyl sebacate (C₁₈H₃₄O₄) in the portion of Dibutyl Sebacate taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of dibutyl sebacate to methyl heptadecanoate from the *Sample solution*

R_S = peak response ratio of dibutyl sebacate to methyl heptadecanoate from the *Standard solution*

C_S = concentration of USP Dibutyl Sebacate RS in the *Standard solution* (mg/mL)

C_U = concentration of Dibutyl Sebacate in the *Sample solution* (mg/mL)

Acceptance criteria: 92.0%–102.0% ■1S (NF31)

SPECIFIC TESTS

- **SPECIFIC GRAVITY** <841>: 0.935–0.939 at 20°
- **REFRACTIVE INDEX** <831>: 1.429–1.441
- **FATS AND FIXED OILS, Acid Value** <401>: NMT 0.1
- **FATS AND FIXED OILS, Saponification Value** <401>: 352–360

ADDITIONAL REQUIREMENTS**Change to read:**

- **PACKAGING AND STORAGE:** Preserve in tight containers.
Store at room temperature. Protect from moisture. ■1S (NF31)

Add the following:

- **USP REFERENCE STANDARDS** <11>
USP Dibutyl Sebacate RS ■1S (NF31)

Gelatin**DEFINITION****Change to read:**

- Purified protein obtained from collagen of animals (including fish and poultry) by partial alkaline and/or acid hydrolysis, by enzymatic hydrolysis, or by thermal hydrolysis. The hydrolysis leads to gelling or non-gelling grades. This monograph covers both the gelling and non-gelling grades as well as hydrolyzed gelatin. ● (RB 1-Apr-2013)

IDENTIFICATION**Change to read:**

- **A.**
Sample solution: Dissolve 1.00 g in carbon dioxide-free water at about 55°, dilute with the same solvent to 100 mL, and keep at 55°. Save the unused portion of this solution for use in the test for pH.
Analysis: To 2 mL of *Sample solution* add 0.05 mL of a 125-g/L solution of copper sulfate pentahydrate. Mix, and add 0.5 mL of an 85-g/L solution of sodium hydroxide.
Acceptance criteria: A violet color is produced. ● (RB 1-Apr-2013)

Change to read:

- **B.**
Sample: 0.5 g
Analysis: Place the *Sample* in a test tube of about 15 mm internal diameter and add 10 mL of water. Allow to stand for 10 min, heat at 60° for 15 min, and keep the tube upright at 0° for 6 h. Invert the tube.
Acceptance criteria: The contents do not flow out immediately for gelling grades. The contents immediately flow out for non-gelling grades. ● (RB 1-Apr-2013)

Add the following:• **C. FOR NON-GELLING GRADES**

Medium: pH 6.8 phosphate buffer. Mix 77.3 mL of a 71.5-g/L solution of disodium hydrogen phosphate dodecahydrate with 22.7 mL of a 21-g/L solution of citric acid.

Sample: 0.5 g

Analysis: Place the *Sample* in a 250-mL bottle. Add 10 mL of water and 5 mL of sulfuric acid. Place the bottle, partly but not completely closed (for example, using a watch glass), in an oven at 105° for 4 h. Allow to cool, and add 200 mL of water. Adjust to a pH of 6.0–8.0 using a 200-g/L solution of sodium hydroxide. Place 2 mL of the solution in a test tube, and add 2 mL of oxidizing reagent (14-g/L solution of chloramine in the *Medium*; prepare immediately before use). Mix, and allow to stand for 20 min. Add 2 mL of color reagent [prepared immediately before use by dissolving 1.0 g of dimethylaminobenzaldehyde in 3.5 mL of perchloric acid (600 g/L of HClO₄) and slowly adding 6.5 mL of 2-propanol]. Mix, and place in a water bath at 60° for about 15 min.

Acceptance criteria: A red color develops. ● (RB 1-Apr-2013)

OTHER COMPONENTS**Delete the following:**• **CONTENT OF SULFUR DIOXIDE**

Sample solution: Dissolve 20.0 g in 150 mL of hot water in a flask having a round bottom and a long neck, add 5 mL of phosphoric acid and 1 g of sodium bicarbonate, and at once connect the flask with a condenser. [NOTE—Excessive foaming can be alleviated by the addition of a few drops of a suitable antifoaming agent.]

Analysis: Distill 50 mL, receiving the distillate under the surface of 50 mL of 0.1 N iodine. Acidify the distillate with a few drops of hydrochloric acid, add 2 mL of barium chloride TS, and heat on a steam bath until the liquid is nearly colorless.

Acceptance criteria: The precipitate of barium sulfate, if any, when filtered, washed, and ignited, weighs NMT 3 mg, corresponding to NMT 40 ppm of sulfur dioxide, correction being made for any sulfate that may be present in 50 mL of the 0.1 N iodine.

Gelatin used in the manufacture of capsules or for the coating of tablets yields NMT 109.3 mg of barium sulfate, corresponding to NMT 0.15% of sulfur dioxide.

● (RB 1-Apr-2013)

IMPURITIES**Delete the following:**• **RESIDUE ON IGNITION <281>**

Sample: 5.0 g

Analysis: Incinerate without the use of sulfuric acid, but with the addition of 1.5–2.0 g of paraffin to avoid loss due to swelling, then finish ashing in a muffle furnace at 550° for 15–20 h.

Acceptance criteria: The weight of the residue does not exceed 2.0%. ● (RB 1-Apr-2013)

Delete the following:• **ARSENIC, Method I <211>**

Solution A: 5 mg/mL of pepsin in 0.1 N hydrochloric acid

Standard solution: Transfer 3.0 mL of *Standard Arsenic Solution* to an arsine generator flask, and dilute with

Solution A to 52 mL. Add 3 mL of hydrochloric acid and 4 mL of isopropyl alcohol.

Sample solution: Mix 3.75 g with 40 mL of *Solution A* in an arsine generator flask. Heat cautiously to a temperature between 65° and 70°, and, while maintaining this temperature for 30 min, sonicate the solution for 2 min at each 10-min interval of heating time. Cool, wash down the sides of the generator with *Solution A*, and dilute with *Solution A* to 52 mL. Add 3 mL of hydrochloric acid and 4 mL of isopropyl alcohol.

Analysis: Proceed as directed in the chapter, except omit the addition of 20 mL of 7 N sulfuric acid and 1 mL of isopropyl alcohol to the *Standard solution* and *Sample solution*.

Acceptance criteria: The resulting solution from the *Sample solution* meets the requirements of the test (NMT 0.8 ppm). ● (RB 1-Apr-2013)

Delete the following:• **HEAVY METALS <231>**

Sample: Residue obtained in the test for *Residue on Ignition*

Analysis: To the *Sample* add 2 mL of hydrochloric acid and 0.5 mL of nitric acid, and evaporate on a steam bath to dryness. To the residue add 1 mL of 1 N hydrochloric acid and 15 mL of water, and warm for a few min. Filter and wash with water to make the filtrate measure 100 mL. Dilute 8 mL of the solution with water to 25 mL.

Acceptance criteria: NMT 50 ppm. ● (RB 1-Apr-2013)

Delete the following:

• **PROCEDURE: ODOR AND WATER-INSOLUBLE SUBSTANCES:** A hot solution (1 in 40) is free from any disagreeable odor, and when viewed in a layer 2-cm thick, is only slightly opalescent. ● (RB 1-Apr-2013)

SPECIFIC TESTS**Add the following:**• **pH**

Sample: Use the *Sample solution* prepared in *Identification* test A.

Acceptance criteria: 3.8–7.6 at 55°. ● (RB 1-Apr-2013)

Add the following:• **WATER CONDUCTIVITY <645>**

Sample: 1.0% solution at 30 ± 1.0°

Analysis: Determine without the use of the temperature compensation.

Acceptance criteria: NMT 1 mS · cm⁻¹. ● (RB 1-Apr-2013)

Add the following:• **SULFUR DIOXIDE**

Sample: 25.0 g

Titrimetric system

Mode: Direct titration

Titrant: 0.1 M sodium hydroxide VS

Endpoint detection: Visual

Analysis: Introduce 150 mL of water into the flask (A) (see *Figure 1*), and pass carbon dioxide through the whole system for 15 min at a rate of 100 mL/min. To 10 mL of hydrogen peroxide solution (30 g/L of H₂O₂) add 0.15 mL of a 1-g/L solution of bromophenol blue in alcohol (20% v/v). Add 0.1 M sodium hydroxide until a violet-blue color is obtained, without exceeding the endpoint. Place the solution in the test tube (D). With-

out interrupting the stream of carbon dioxide, remove the funnel (B), and introduce through the opening into the flask (A) the *Sample* with the aid of 100 mL of water. Add through the funnel 80 mL of dilute hydrochloric acid (73 g/L of HCl), and boil for 1 h. Open the tap of the funnel, stop the flow of carbon dioxide, and also stop the heating and the cooling water. Transfer the contents of the test tube with the aid of a little water to a 200-mL wide-necked, conical flask. Heat on a water bath for 15 min, and allow to cool. Add 0.1 mL of a 1-g/L solution of bromophenol blue in alcohol (20% v/v), and titrate with *Titrant* until the color changes from yellow to violet-blue.

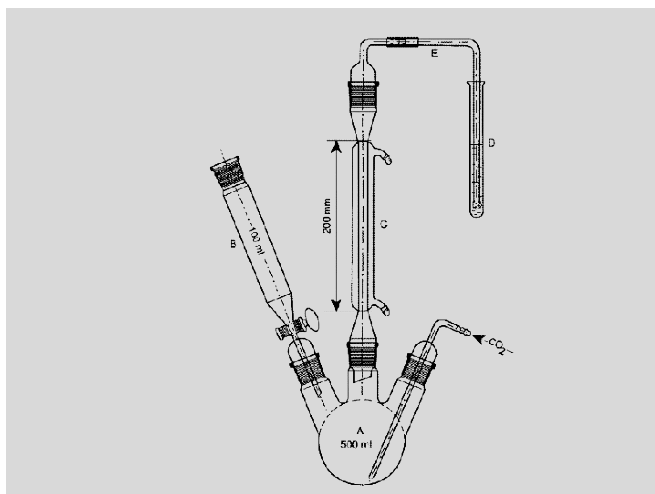


Figure 1. Apparatus for determination of sulfur dioxide.

Carry out a blank titration, and calculate the content of sulfur dioxide, in ppm:

$$\text{Result} = [(V_1 - V_2) \times m/W] \times 32,030$$

V_1 = volume of 0.1 M sodium hydroxide consumed by the *Sample* (mL)

V_2 = volume of 0.1 M sodium hydroxide consumed by the blank (mL)

m = actual molarity of the *Titrant* (mol/mL)

W = weight of the *Sample* (g)

Acceptance criteria: NMT 50 ppm • (RB 1-Apr-2013)

Add the following:

• PEROXIDES

Peroxidase transfers oxygen from peroxides to an organic redox indicator which is converted to a blue oxidation product. The intensity of the color obtained is proportional to the quantity of peroxide, and can be compared with a color scale provided with the test strips to determine the peroxide concentration.

Peroxide test strips: Use commercial test strips with a suitable scale covering the range of 0–25 ppm of peroxide.

Sample: 20.0 ± 0.1 g

Suitability test: Dip a test strip for 1 s into hydrogen peroxide standard solution (10 ppm of H_2O_2) [prepared by dilution of hydrogen peroxide solution (30 g/L of H_2O_2)], such that the reaction zone is properly wetted. Remove the test strip, shake off excess liquid, and after 15 s compare the reaction zone with the color scale provided. The test strips are suitable if the color matches that of the 10 ppm concentration.

Analysis: Weigh the *Sample* in a beaker, and add 80.0 ± 0.2 mL of water. Stir to moisten all the gelatin, and allow the sample to stand at room temperature for 1–3 h. Cover the beaker with a watch glass. If the sam-

ple is not dissolved completely, place the beaker in a water bath at $65 \pm 2^\circ$ for 20 ± 5 min to dissolve the sample. Stir the contents of the beaker with a glass rod to achieve a homogeneous solution. Dip a test strip for 1 s into the test solution, such that the reaction zone is properly wetted. Remove the test strip, shake off excess liquid, and after 15 s compare the reaction zone with the color scale provided. Multiply the concentration read from the color scale by a factor of 5 to calculate the concentration, in ppm, of peroxide in the test substance.

Acceptance criteria: NMT 10 ppm • (RB 1-Apr-2013)

Add the following:

• GEL STRENGTH (BLOOM VALUE)

For gelling grades

The gel strength is expressed as the mass in grams necessary to produce the force which, applied to a plunger 12.7 mm in diameter, makes a depression 4 mm deep in a gel having a concentration of 6.67% m/m and matured at 10° .

Sample: 7.5 g

Apparatus: Texture analyzer or gelometer with a cylindrical piston 12.7 ± 0.1 mm in diameter with a plane pressure surface and a sharp bottom edge, and a bottle 59 ± 1 mm in internal diameter and 85 mm high. Adjust the apparatus according to the manufacturer's manual.

Settings

Distance: 4 mm

Test speed: 0.5 mm/s

Analysis: Place the *Sample* in a bottle. Add 105 mL of water, place a watch glass over the bottle, and allow to stand for 1–4 h. Heat in a water bath at $65 \pm 2^\circ$ for 15 min. While heating, stir gently with a glass rod. Ensure that the solution is uniform and that any condensed water on the inner walls of the bottle is incorporated. Allow to cool at room temperature for 15 min, and transfer the bottle to a thermostatically controlled bath at $10.0 \pm 0.1^\circ$, fitted with a device to ensure that the platform on which the bottle stands is perfectly horizontal. Close the bottle with a rubber stopper, and allow to stand for 17 ± 1 h. Remove the sample bottle from the bath, and quickly wipe the water from the exterior of the bottle. Center the bottle on the platform of the apparatus so that the plunger contacts the sample as nearly at its midpoint as possible, and start the measurement.

Acceptance criteria: 80%–120% of the labeled nominal value • (RB 1-Apr-2013)

Add the following:

• IRON

Atomic absorption spectrometry, standard additions method

Test solution: In a conical flask add 10 mL of hydrochloric acid (37% m/m of HCl) to 5.00 g of the substance to be examined. Close the flask, and place in a water bath at 75° – 80° for 2 h. (If necessary for proper solubilization, the gelatin may be allowed to swell after addition of the acid and before heating, the heating time may be prolonged, and a higher temperature may be used.) Allow to cool, and adjust the contents of the flask with water to 100.0 g.

Iron standard solution (8 ppm): Dissolve 80 mg of iron in 50 mL of hydrochloric acid (220 g/L of HCl), and dilute with water to 1000.0 mL. Immediately before use, prepare a 1:10 dilution with water.

Reference solutions: Prepare the reference solutions using the *Iron standard solution*, diluted with water as necessary.

Instrumental conditions(See *Spectrophotometry and Light-Scattering* (851).)**Analytical wavelength:** 248.3 nm**Acceptance criteria:** NMT 30 ppm • (RB 1-Apr-2013)**Add the following:**• **CHROMIUM**

Atomic absorption spectrometry, standard additions method

Test solution: Use the *Test solution* described in the test for *Iron*.**Chromium standard solution** (100 ppm): 0.283 mg/mL of $K_2Cr_2O_7$ in water**Reference solutions:** Prepare the reference solutions using the *Chromium standard solution*, diluted with water if necessary.**Instrumental conditions**(See *Spectrophotometry and Light-Scattering* (851).)**Analytical wavelength:** 357.9 nm**Acceptance criteria:** NMT 10 ppm • (RB 1-Apr-2013)**Add the following:**• **ZINC**

Atomic absorption spectrometry, standard additions method

Test solution: Use the *Test solution* described in the test for *Iron*.**Zinc standard solution** (10 ppm): Dissolve 0.440 g of zinc sulfate heptahydrate and 1 mL of acetic acid (300 g/L of $C_2H_4O_2$) in water, and dilute to 100.0 mL. Immediately before use, prepare a 1:100 dilution in water.**Reference solutions:** Prepare the reference solutions using the *Zinc standard solution*, diluted if necessary with water.**Instrumental conditions**(See *Spectrophotometry and Light-Scattering* (851).)**Analytical wavelength:** 213.9 nm**Acceptance criteria:** NMT 30 ppm • (RB 1-Apr-2013)**Add the following:**• **LOSS ON DRYING (731)****Sample:** 5.0 g**Analysis:** Dry the *Sample* in an oven at 105° for 16 h.**Acceptance criteria:** NMT 15% • (RB 1-Apr-2013)**Change to read:**

• **MICROBIAL ENUMERATION TESTS (61) and TESTS FOR SPECIFIED MICROORGANISMS (62):** The total bacterial count does not exceed 10^3 cfu/g, the total yeasts and molds count does not exceed 10^2 cfu/g, • (RB 1-Apr-2013) and the tests for *Salmonella* species and *Escherichia coli* are negative.

ADDITIONAL REQUIREMENTS**Delete the following:**

• **PACKAGING AND STORAGE:** Preserve in well-closed containers in a dry place. • (RB 1-Apr-2013)

Add the following:

• **STORAGE:** Protect from heat and moisture. • (RB 1-Apr-2013)

Add the following:

• **LABELING:** The label states the *Gel Strength (Bloom Value)* or that it is a non-gelling grade. • (RB 1-Apr-2013)

Isobutane C_4H_{10}

58.12

DEFINITIONIsobutane contains NLT 95.0% of isobutane (C_4H_{10}).[**CAUTION**—Isobutane is highly flammable and explosive.]**IDENTIFICATION**

- **A. IR ABSORPTION:** Exhibits maxima, among others, at about the following wavelengths (μm): 3.4 (vs), 6.8 (s), 7.2 (m), 8.5 (m), and 10.9 (m).
- **B.** The vapor pressure of a test specimen obtained as directed for *Propellants* (in *Aerosols*, *Nasal Sprays*, *Metered-Dose Inhalers*, and *Dry Powder Inhalers* (601), *General Sampling Procedures*), and determined at 21° by means of a suitable pressure gauge, is between 303 and 331 kPa absolute (44 and 48 psia).

ASSAY**Change to read:**• **PROCEDURE****Chromatographic system**(See *Chromatography* (621), *System Suitability*.)**Mode:** GC**Detector:** Thermal conductivity**Column:** 3-mm \times 6-m aluminum; packed with 10 weight percent of liquid phase G30 on support S1D-15 (NF31)**Column temperature:** 33°**Carrier gas:** Helium**Flow rate:** 50 mL/min**Injection volume:** 2 μ L**System suitability****Sample:** Isobutane**Suitability requirements****Sample response comparison:** Peak responses for isobutane from duplicate injections agree within 1%.**Analysis****Sample:** Isobutane

Connect one Isobutane cylinder to the chromatograph through a suitable sampling valve and a flow control valve downstream from the sampling valve. Flush the liquid specimen through the sampling valve, taking care to avoid entrapment of gas or air in the sampling valve.

Calculate the percentage purity of Isobutane:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of isobutane
 r_T = sum of all the peak responses

Acceptance criteria: NLT 95.0%

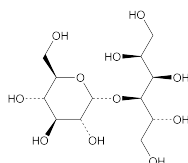
SPECIFIC TESTS

- **WATER:** NMT 0.001%, determined as directed in *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* (601), *Water Content*
- **HIGH-BOILING RESIDUES:** NMT 5 µg/mL, determined as directed in *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* (601), *High-Boiling Residues, Method II*
- **ACIDITY OF RESIDUE**
Sample: Residue from the test for *High-Boiling Residues*
Analysis: Add 10 mL of water to the *Sample*, mix by swirling for about 30 s, add 2 drops of methyl orange TS, insert the stopper in the tube, and shake vigorously.
Acceptance criteria: No pink or red color appears in the aqueous layer.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight cylinders, and prevent exposure to excessive heat.

Maltitol



C₁₂H₂₄O₁₁

D-Glucopyranosyl-D-glucitol [585-88-6].

344.31

DEFINITION

Maltitol contains NLT 92.0% and NMT 100.5% of D-maltitol (C₁₂H₂₄O₁₁), calculated on the anhydrous basis. The amounts of total sugars, other polyhydric alcohols, and any polyol anhydrides, if detected, are not included in the requirements or in the calculated amount in *General Notices and Requirements*, 5.60.10 *Other Impurities in USP and NF Articles*.

IDENTIFICATION

Delete the following:

• A. PROCEDURE

Sample solution: 1 g of Maltitol in 75 mL of water

Analysis: Transfer 3 mL of the *Sample solution* to a 15-cm test tube, and add 3 mL of freshly prepared catechol solution (1 in 10). Add 6 mL of sulfuric acid, mix again, and gently heat the tube in a flame for 30 s.

Acceptance criteria: A deep pink or wine-red color appears. ■^{1S} (NF31)

Add the following:

• A. INFRARED ABSORPTION (197K) ■^{1S} (NF31)

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

• PROCEDURE

Mobile phase: Water. [NOTE—Degas the *Mobile phase* before use.]

System suitability solution: 4.8 mg/g of USP Maltitol RS and 4.8 mg/g of sorbitol

Standard solution: 10 mg/g of USP Maltitol RS and 1.6 mg/g of sorbitol

Sample solution: Dissolve 0.20 g of Maltitol in water, and dilute with water to 20 g. Record the final solution weight, and mix thoroughly. The solution is 10 mg/g of Maltitol.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: Refractive index

Column: 7.8-mm × 10-cm; packing L34

Temperatures

Column: 60 ± 2°

Detector: 35°

Flow rate: 0.5 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for maltitol and sorbitol are 0.48 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between maltitol and sorbitol, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of D-maltitol (C₁₂H₂₄O₁₁) in the portion of Maltitol taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [100/(100 - W)] \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Maltitol RS in the *Standard solution* (mg/g)

C_U = concentration of Maltitol in the *Sample solution* (mg/g)

W = percentage obtained in the test for *Water Determination*

Acceptance criteria: 92.0%–100.5% on the anhydrous basis

IMPURITIES

• LIMIT OF NICKEL

Sample solution: Dissolve 20.0 g of Maltitol in diluted acetic acid, and dilute with diluted acetic acid to 150 mL.

Blank solution: 150 mL of diluted acetic acid

Standard solutions: Prepare three solutions by adding 0.5, 1.0, and 1.5 mL of nickel standard solution TS to 20.0 g of Maltitol dissolved in diluted acetic acid, and dilute with the same solvent to 150 mL.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: Atomic absorption spectrophotometry

Analytical wavelength: Maxima at about 232.0 nm

Lamp: Nickel hollow-cathode

Flame: Air–acetylene

Analysis

Samples: *Standard solutions* and *Sample solution*

To each sample, add 2.0 mL of a saturated ammonium pyrrolidinedithiocarbamate solution (containing 10 g/L of ammonium pyrrolidinedithiocarbamate) and 10.0 mL of methyl isobutyl ketone, and shake for 30 s. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer. Set the instrument to zero using the organic layer from the *Blank solution*. Concomitantly determine the absorbances of the organic layer from the *Samples* at least three times each. Record the average of the steady readings for each of the *Standard solutions* and the *Sample solution*. Between each measurement, aspirate the organic layer from the *Blank solution*, and as-

certain that the reading returns to zero. Plot the absorbances of the *Standard solutions* and the *Sample solution* versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the *Sample solution*.

Acceptance criteria: NMT 1 µg/g

• **REDUCING SUGARS**

Sample: 3.3 g

Titrimetric system

Mode: Residual titration

Titrant: 0.05 N sodium thiosulfate VS

Endpoint detection: Visual

Analysis: Dissolve the *Sample* in 3 mL of water with the aid of gentle heat. Cool, and add 20.0 mL of cupric citrate TS and a few glass beads. Heat so that boiling begins after 4 min, and maintain boiling for 3 min. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of hydrochloric acid in water solution (6:94). When the precipitate has dissolved, titrate the excess of iodine with *Titrant* using 2 mL of starch TS, added towards the end of the titration, as an indicator.

Acceptance criteria: NLT 12.8 mL of *Titrant* is required, corresponding to NMT 0.3% of reducing sugars, as glucose. [NOTE—The amount determined in this test is not included in the calculated amount in *General Notices and Requirements*, 5.60.10 *Other Impurities in USP and NF Articles*.]

SPECIFIC TESTS

• **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count using the *Plate Method* does not exceed 10^3 cfu/g, and the total combined molds and yeasts count does not exceed 10^2 cfu/g.

• **CONDUCTIVITY**

Sample solution: 200 mg/mL

Analysis: Using an appropriate conductivity meter, choose a conductivity cell that is appropriate for the properties and conductivity of the solution to be examined. Use a certified reference material, for example a solution of potassium chloride, that is appropriate for the measurement.¹

The conductivity value of the certified reference material should be near the expected conductivity value of the solution to be examined. After calibrating the apparatus with a certified reference material solution, rinse the conductivity cell several times with water and at least twice with the aqueous solution to be examined. Measure the conductivity of the *Sample solution* at a temperature of 20°, while gently stirring with a magnetic stirrer.

Acceptance criteria: NMT 20 µS/cm

• **WATER DETERMINATION, Method I** (921): NMT 1.0%

ADDITIONAL REQUIREMENTS

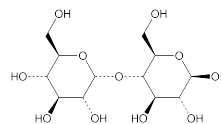
• **PACKAGING AND STORAGE:** Preserve in well-closed containers. No storage requirements are specified.

• **USP REFERENCE STANDARDS** (11)

USP Maltitol RS

¹ Commercially available conductivity calibration solutions for conductivity meter standardization, standardized by methods traceable to the National Institute of Standards and Technology (NIST), may be used. Solutions prepared according to the instructions given in ASTM Standard D1125 may be used, provided the conductivity of the resultant solution is the same as that of the solution prepared from the NIST-certified material.

Maltose



$C_{12}H_{22}O_{11} \cdot H_2O$ 360.31

$C_{12}H_{22}O_{11}$ 342.30

4-O-α-D-Glucopyranosyl-β-D-glucopyranose [69-79-4].

4-O-α-D-Glucopyranosyl-β-D-glucopyranose monohydrate [6363-53-7].

DEFINITION

Maltose is a sugar. It contains one molecule of water of hydration or is anhydrous. It contains NLT 92.0% of maltose, calculated on the anhydrous basis. The amounts of other sugars, if detected, are not included in the requirements or the calculated amount in *General Notices and Requirements*, 5.60.10 *Other Impurities in USP and NF Articles*.

IDENTIFICATION

Change to read:

• **A.** ■Perform this test for Anhydrous Maltose only. ■1S (NF31)

Sample solution: 50 mg/mL

Analysis: Add 2–3 drops of the *Sample solution* to 5 mL of hot alkaline cupric tartrate TS.

Acceptance criteria: A red precipitate is formed.

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

Add the following:

■ **C. INFRARED ABSORPTION** (197K): Perform the test for Maltose Monohydrate only. Use the undried sample and USP Maltose Monohydrate RS. ■1S (NF31)

ASSAY

• **PROCEDURE**

Mobile phase: Water

System suitability solution: 10 mg/g each of maltotriose, maltose, and glucose

Standard solution: Dissolve USP Maltose Monohydrate RS in water to obtain a solution having a concentration of about 10 mg/g. Calculate the exact concentration on the anhydrous basis.

Sample solution: Dissolve 0.10 g of Maltose in water, and dilute with water to 10 g. Record the final solution weight, and mix thoroughly.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: Refractive index

Column: 7.8-mm × 30-cm; packing L58

Temperatures

Column: $80 \pm 2^\circ$

Detector: 40°

Flow rate: 0.35 mL/min; adjust so that the resolution between maltotriose and maltose is NLT 1.6.

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for maltotriose, maltose, and glucose are about 0.9, 1.0, and 1.2, respectively.]

Suitability requirements

Resolution: NLT 1.6 between maltotriose and maltose, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate, on the anhydrous basis, the percentage of Maltose taken:

$$\text{Result} = [(r_U/r_S) \times (C_S/C_U)] / [(100 - W)/100] \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Maltose Monohydrate RS in the *Standard solution*, on the anhydrous basis (mg/g)

C_U = concentration of Maltose in the *Sample solution* (mg/g)

W = percentage of water from the test for *Water Determination*

Acceptance criteria: NLT 92.0% on the anhydrous basis

IMPURITIES

- RESIDUE ON IGNITION** (281)

Sample: 2 g

Acceptance criteria: NMT 0.05%

- HEAVY METALS, Method I** (231): NMT 5 µg/g

SPECIFIC TESTS

- DEXTRIN, STARCH, AND SULFITE**

Sample solution: 1.0 g of Maltose in 10 mL of water

Analysis: Add 1 drop of iodine TS to the *Sample solution*.

Acceptance criteria: A yellow color develops. Then add 1 drop of starch TS; a blue color develops.

- PH** (791)

Sample solution: 100 mg/mL in carbon dioxide-free water

Acceptance criteria

Anhydrous form: 3.7–4.7

Monohydrate form: 4.0–5.5

- WATER DETERMINATION, Method I** (921)

Anhydrous: NMT 1.5%

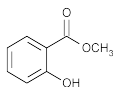
Monohydrate: 4.5%–6.5%

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in well-closed containers. No storage requirements specified.

- USP REFERENCE STANDARDS** (11)

USP Maltose Monohydrate RS

Methyl Salicylate

$C_8H_8O_3$

Benzoic acid, 2-hydroxy-, methyl ester;
Methyl salicylate [119-36-8].

152.15

DEFINITION

Methyl Salicylate is produced synthetically or is obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* L. (Fam. Ericaceae) or from the bark of *Betula lenta* L. (Fam. Betulaceae). It contains NLT 98.0% and NMT 100.5% of methyl salicylate ($C_8H_8O_3$).

IDENTIFICATION**Change to read:**

- A. ■INFRARED ABSORPTION** (197F)■15 (NF31)

ASSAY

- PROCEDURE**

Sample: 2 g of Methyl Salicylate

Titrimetric system

(See *Titrimetry* (541).)

Mode: Residual titration

Titrant: 1 N sodium hydroxide VS

Back-titrant: 1 N sulfuric acid VS

Endpoint detection: Colorimetric

Analysis: Place the *Sample* in a flask, and add 40.0 mL of *Titrant*. Boil gently under a reflux condenser for 2 h. Cool, rinse the condenser and the sides of the flask with a few mL of water, and add phenolphthalein TS. Titrate the excess alkali with *Back-titrant*. Perform a blank determination. Each mL of 1 N sodium hydroxide VS corresponds to 152.2 mg of methyl salicylate ($C_8H_8O_3$).

Acceptance criteria: 98.0%–100.5%

IMPURITIES

- HEAVY METALS, Method II** (231): NMT 20 µg/g

SPECIFIC TESTS

- SOLUBILITY IN 70% ALCOHOL:** One volume of synthetic Methyl Salicylate dissolves in seven volumes of 70% alcohol. One volume of natural Methyl Salicylate dissolves in seven volumes of 70% alcohol, the solution having NMT a slight cloudiness.

- SPECIFIC GRAVITY** (841): 1.180–1.185 for the synthetic variety; 1.176–1.182 for the natural variety

- OPTICAL ROTATION, Angular Rotation** (781A): Synthetic Methyl Salicylate and that from *Betula* are optically inactive. Methyl Salicylate from *Gaultheria* is slightly levorotatory, the angular rotation not exceeding -1.5° in a 100-mm tube.

- REFRACTIVE INDEX** (831): 1.535–1.538 at 20°

ADDITIONAL REQUIREMENTS

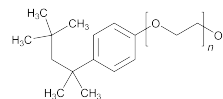
- PACKAGING AND STORAGE:** Preserve in tight containers.

- LABELING:** Label it to indicate whether it was made synthetically or distilled from either of the plants of *Gaultheria procumbens* or *Betula lenta*.

Add the following:

- USP REFERENCE STANDARDS** (11)

USP Methyl Salicylate RS■15 (NF31)

Octoxynol 9**Change to read:**

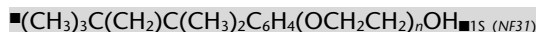
■Poly(oxy-1,2-ethanediyl), α -[4-(1,1,3,3-tetramethylbutyl)phenyl]- ω -hydroxy-;
 α -[4-(1,1,3,3-tetramethylbutyl)phenyl]- ω -hydroxypoly(oxy-1,2-ethanediyl);
Polyethylene glycol mono[p -(1,1,3,3-tetramethylbutyl)phenyl] ether;

Polyethylene glycol mono(4-*tert*-octylphenyl) ether \blacksquare_{1S} (NF31)
[9002-93-1].

DEFINITION

Change to read:

Octoxynol 9 is an anhydrous liquid mixture consisting chiefly of \blacksquare mono[*p*-(1,1,3,3-tetramethylbutyl)]phenyl \blacksquare_{1S} (NF31) ethers of polyethylene glycols, corresponding to:



in which the average value of *n* is about 9. \blacksquare It contains NLT 90.0% and NMT 110.0% of Octoxynol 9. \blacksquare_{1S} (NF31)

IDENTIFICATION

Change to read:

- $\blacksquare_{A,1S}$ (NF31) **INFRARED ABSORPTION** (197F): On undried specimen

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. \blacksquare_{1S} (NF31)

ASSAY

Add the following:

PROCEDURE

Mobile phase: Methanol:water (4:1)

Standard solution: 25 mg/mL of USP Octoxynol 9 RS in *Mobile phase*

System suitability solution: 25 mg/mL of USP Octoxynol 9 RS and 25 mg/mL of USP Nonoxynol 9 RS in *Mobile phase*

Sample solution: 25 mg/mL of Octoxynol 9 in *Mobile phase*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm \times 25-cm, 5- μ m packing L1

Column temperature: Ambient

Flow rate: 1.0 mL/min

Injection size: 10 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for octoxynol 9 and nonoxynol 9 are 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 2.0 between octoxynol 9 and nonoxynol 9, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms, and measure the responses for octoxynol 9, including any shoulders and bumps. Calculate the percentage of octoxynol 9 in the portion of test specimen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of octoxynol 9 from the *Sample solution*

r_S = peak response of octoxynol 9 from the *Standard solution*

C_S = concentration of USP Octoxynol 9 RS in the *Standard solution* (mg/mL)

C_U = concentration of Octoxynol 9 in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% \blacksquare_{1S} (NF31)

Add the following:

CONTENT OF FREE POLYETHYLENE GLYCOLS

Sample: 10 g

Analysis: Transfer the *Sample* to a 250-mL beaker. Add 100 mL of ethyl acetate, and stir on a magnetic stirrer to make a solution. Transfer, with the aid of 100 mL of 5 N sodium chloride, to a pear-shaped, 500-mL separator fitted with a glass stopper. Insert the stopper, and shake vigorously for 1 min. Remove the stopper carefully to release the pressure. Immerse a thermometer in the mixture, and support the separator so that it is partially immersed in a water bath maintained at 50°. Swirl the separator gently while letting the internal temperature rise to 40°–45°. Immediately remove the separator from the bath, dry the outside surface, and drain the salt (lower) layer into another pear-shaped, 500-mL separator. In the same manner, extract the ethyl acetate layer a second time with 100 mL of fresh 5 N sodium chloride, combining the two aqueous extracts. Discard the ethyl acetate layer.

Wash the combined aqueous layers with 100 mL of ethyl acetate, using the same technique, and drain the salt (lower) layer into a clean pear-shaped, 500-mL separator. Discard the ethyl acetate layer.

Extract the aqueous layer with two successive 100-mL portions of chloroform, draining the chloroform (lower) layers through Whatman folded filter paper 2V, and combining them into a 250-mL beaker.

Evaporate on a steam bath or with a rotary evaporator to dryness, and continue heating to remove chloroform. Allow the beaker to cool. Add 25 mL of acetone, and dissolve the residue on a magnetic stirrer. Pass through Whatman folded filter paper 2V into a tared 250-mL beaker, rinsing with two 25-mL portions of acetone. Evaporate on a steam bath or with a rotary evaporator to dryness. Dry in vacuum at 60° for 1 h. Allow the beaker to cool, and weigh.

Acceptance criteria: NMT 1.0% of polyethylene glycol \blacksquare_{1S} (NF31)

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.4%

- **HEAVY METALS** (231): NMT 20 ppm

- **LIMIT OF FREE ETHYLENE OXIDE**

Stripped octoxynol 9: Maintain Octoxynol 9 at a temperature of 150° with constant stirring in an open vessel until it no longer displays a peak for ethylene oxide when chromatographed as directed below.

Standard stock solution: [NOTE—Ethylene oxide is toxic and flammable. Prepare these solutions in a well-ventilated hood, using great care.] Chill all apparatus and reagents used in the preparation of standards in a refrigerator or freezer before use. Fill a chilled pressure bottle with liquid ethylene oxide from a lecture bottle, and store in a freezer when not in use. Use a small piece of polyethylene film to protect the liquid from contact with the rubber gasket. Transfer about 100 mL of chilled isopropyl alcohol to a 500-mL volumetric flask. Using a chilled graduated cylinder, transfer 25 mL of ethylene oxide to the isopropyl alcohol, and swirl gently to mix. Dilute with additional chilled isopropyl alcohol to volume, replace the stopper, and swirl gently to mix. This stock solution contains about 43.6 mg/mL of ethylene oxide.

Standard solutions: Pipet 25 mL of 0.5 N alcoholic hydrochloric acid, prepared by mixing 45 mL of hydrochloric acid with 1 L of alcohol, into a 500-mL conical flask containing 40 g of magnesium chloride hexahydrate. Shake the mixture to effect saturation. Pipet 10 mL of the *Standard stock solution* into the flask, and add 20 drops of bromocresol green TS. If the solution is not yellow (acid), add an additional volume, accurately measured, of 0.5 N alcoholic hydrochloric acid to give an excess of about 10 mL. Record the total volume of 0.5 N alcoholic hydrochloric acid added. Insert the stopper into the flask, and allow to stand for 30 min. Titrate the excess acid with 0.5 N alcoholic potassium hydroxide VS. Perform a blank titration, using 10.0 mL of isopropyl alcohol instead of *Standard stock solution*, adding the same total volume of 0.5 N alcoholic hydrochloric acid, and note the difference in volumes required. Each mL of the difference in volumes of 0.5 N alcoholic potassium hydroxide consumed is equivalent to 22.02 mg of ethylene oxide. Calculate the concentration, in mg/mL, of ethylene oxide in the *Standard stock solution*. Standardize daily. Store in a refrigerator. Prepare a 1000-ppm standard by pipeting into a container the calculated volume (about 2 mL) of cold *Standard stock solution* that on the basis of the standardization contains 88.6 mg of ethylene oxide, and adding 87.0 g of *Stripped octoxynol 9*. Prepare 10-, 5-, and 0.5-ppm standards by quantitatively diluting the 1000-ppm standard with additional *Stripped octoxynol 9*.

Standard solution 0.5 ppm: Transfer 5 ± 0.01 g of the *Standard solution* containing 0.5 ppm ethylene oxide to suitable serum vials equipped with pressure-tight septum closures designed to relieve any excessive pressure, and seal them.

Standard solution 5 ppm: Transfer 5 ± 0.01 g of the *Standard solution* containing 5 ppm ethylene oxide to suitable serum vials equipped with pressure-tight septum closures designed to relieve any excessive pressure, and seal them.

Standard solution 10 ppm: Transfer 5 ± 0.01 g of the *Standard solution* containing 10 ppm ethylene oxide to suitable serum vials equipped with pressure-tight septum closures designed to relieve any excessive pressure, and seal them.

System suitability solution: 10 µg/mL of ethylene oxide and 10 µg/mL of acetaldehyde in *Stripped octoxynol 9*.

Sample solution: Transfer 5 ± 0.01 g of Octoxynol 9 to a serum vial of the same kind as the vials used for *Standard solution A*.

Chromatographic system
(See *Chromatography* (621), *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 2.1-mm × 6.4-m nickel; 60- to 80-mesh support S9 (under typical conditions)

Temperature

Column: 100°

Injector: 160°

Detector: 200°

Carrier gas: Helium

Flow rate: 30 mL/min

System suitability

Samples: *System suitability solution*, *Standard solution 0.5 ppm*, *Standard solution 5 ppm*, and *Standard solution 10 ppm*

Suitability requirements

Resolution: NLT 1.5 between ethylene oxide and acetaldehyde, *System suitability solution*

Calibration: None of the points used for constructing the straight line *Calibration curve* deviates from the line by more than 10%, *Standard solution 0.5 ppm*, *Standard solution 5 ppm*, *Standard solution 10 ppm*.

Analysis

Samples: *System suitability solution*, *Standard solution 0.5 ppm*, *Standard solution 5 ppm*, *Standard solution 10 ppm*, and *Sample solution*

Calibration: Place the vial containing *Standard solution 10 ppm* in an oven, and heat at 90° for 30 min. Remove the vial from the oven. Using a gas-tight syringe, immediately inject a 100-µL aliquot of the headspace gas into the gas chromatograph. Obtain the area for the ethylene oxide peak (retention time approximately 8 min). Raise the temperature of the column to 200° after ethylene oxide elutes to volatilize heavy components. Re-equilibrate the column at 100°. Repeat the foregoing steps, using the vials containing *Standard solution 0.5 ppm* and *Standard solution 5 ppm*. On linear graph paper, plot area units versus ppm ethylene oxide for the standards, and draw the best straight line through the points.

Place the vial containing the *Sample solution* in an oven, and heat at 90° for 30 min. Remove the vial from the oven. Immediately inject a 100-µL aliquot of the headspace gas into the gas chromatograph, and obtain the area for the ethylene oxide peak.

Calculate the concentration of ethylene oxide in the sample, in ppm:

$$\text{Result} = r_U \times S$$

r_U = peak area from the *Sample solution*

S = slope of the standard curve (ppm/peak area unit)

Acceptance criteria: NMT 5 ppm

• LIMIT OF DIOXANE

Apparatus: Assemble a closed-system vacuum distillation apparatus, using glass vacuum stopcocks (A, B, and C), as shown in *Figure 1*. The concentrator tube (D)¹ is made of borosilicate or quartz (not flint) glass, graduated precisely enough to measure the 0.9 mL or more of distillate collected and marked so that the analyst can dilute accurately to 2.0 mL.

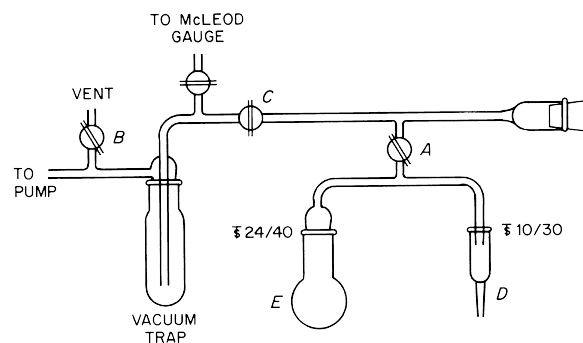


Figure 1. Closed-system vacuum distillation apparatus for dioxane.

Standard solution: 100 µg/mL of dioxane in water. Use a freshly prepared solution.

Sample solution: Transfer 20.0 g to a 50-mL round-bottom flask (E) having a 24/40 ground-glass neck joint. Add 1.0 mL of water. Place a small polytetrafluoroethylene-covered stirring bar in the flask, insert the stopper, and stir to mix. Immerse the flask in an ice bath, and chill for 1 min. Wrap heating tape around the tube connecting the concentrator tube (D) and the round-bottom flask, and apply 10 V to the tape. Apply a light coating of high-vacuum silicone grease to the ground-glass joints, and connect the concentrator tube to the 10/30 joint and the round-bottom flask to the 24/40 joint. Immerse the

¹ A suitable tube is available as Chromaflex concentrator tube, Kontes Glass Co., Vineland, NJ (Catalog No. K42560-0000).

vacuum trap in a Dewar flask filled with liquid nitrogen, close stopcocks A and B, open stopcock C, and begin evacuating the system with a vacuum pump. Prepare a slurry bath from powdered dry ice and methanol, and raise the bath to the neck of the round-bottom flask. After freezing the contents of the flask for 10 min, and when the vacuum system is operating at a 0.05-mm pressure or lower, open stopcock A for 20 s, then close it. Remove the slurry bath, and allow the flask to warm in air for 1 min. Immerse the flask in a water bath maintained at a temperature of 20°–25°, and after about 5 min warm the water bath to 35°–40° (sufficient to liquefy most specimens) while stirring slowly but constantly with the magnetic bar. Cool the water in the bath by adding ice, and chill for about 2 min. Replace the water bath with the slurry bath, freeze the contents of the round-bottom flask for 10 min, open stopcock A for 20 s, and then close it. Remove the slurry bath, and repeat the heating steps as before, this time reaching a final temperature of 45°–50° or a temperature necessary to melt the specimen completely. If there is any condensation in the tube connecting the round-bottom flask to the concentrator tube, slowly increase the voltage to the heating tape, and heat until the condensation disappears.

Stir with the magnetic stirrer throughout the following steps. Very slowly immerse the concentrator tube in a Dewar flask containing liquid nitrogen.

[CAUTION]—When there is liquid distillate in the concentrator tube, immerse the tube in the liquid nitrogen very slowly, or the tube will break.]

Water will begin to distill into the concentrator tube. As ice forms in the concentrator tube, raise the Dewar flask to keep the liquid nitrogen level only slightly below the level of ice in the tube. When water begins to freeze in the neck of the 10/30 joint, or when liquid nitrogen reaches the 2.0-mL graduation mark on the concentrator tube, remove the Dewar flask, and allow the ice to melt without heating. After the ice has melted, check the volume of water that has distilled, and repeat the sequence of chilling and thawing until NLT 0.9 mL of water has been collected. Freeze the tube once again for about 2 min, and release the vacuum first by opening stopcock B, followed by opening stopcock A. Remove the concentrator tube from the apparatus, close it with a greased stopper, and allow the ice to melt without heating. Mix the contents of the concentrator tube by swirling, note the volume of distillate, and dilute with water to 2.0 mL, if necessary.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 2-mm × 1.8-m glass; support S10 (under typical conditions)

Temperature

Column: 140°

Injector: 200°

Detector: 250°

Carrier gas: Nitrogen or helium

Flow rate: 35 mL/min

Install an oxygen scrubber between the carrier gas line and the column. Condition the column for 72 h at 230° with 30–40 mL/min carrier flow. [NOTE—Support S10 is oxygen-sensitive. Each time a column is installed, flush with carrier gas for 30–60 min before heating.]

Injection size: 2–4 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Acceptance criteria: The height of the peak from the *Sample solution* is NMT that from the *Standard solution*: NMT 10 µg/g (ppm).

SPECIFIC TESTS

Delete the following:

• CLOUD POINT

Analysis: Weigh 1.00 g into a 250-mL beaker, and add 99 g of water. Dissolve completely by careful heating, while stirring at a constant, slow speed with a small-propeller-blade stirrer. Center a thermometer vertically in the solution, and heat rapidly until the entire solution becomes cloudy, then raise the temperature 10°. Remove the source of heat, continue stirring, and record the temperature at which the solution becomes sufficiently clear to permit seeing the entire thermometer bulb plainly.

Acceptance criteria: 63–69°.■1S (NF31)

Add the following:

• **FATS AND FIXED OILS, Acid Value <401>:** NMT 0.2.■1S (NF31)

• **FATS AND FIXED OILS, Hydroxyl Value <401>:** 85–101

Add the following:

• **FATS AND FIXED OILS, Peroxide Value <401>:** NMT 10.0.■1S (NF31)

• **WATER DETERMINATION, Method I <921>:** NMT 0.5%

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight containers.
■Store at room temperature.■1S (NF31)

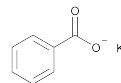
Change to read:

• **USP REFERENCE STANDARDS <11>**

■USP Nonoxynol 9 RS.■1S (NF31)

USP Octoxynol 9 RS

Potassium Benzoate



C₇H₅KO₂

160.21

Benzoic acid, potassium salt;

Potassium benzoate [582-25-2].

DEFINITION

Change to read:

Potassium Benzoate contains NLT 99.0% and NMT

■101.0%.■1S (NF31) of potassium benzoate (C₇H₅KO₂), calculated on the anhydrous basis.

Analysis: Determine the vapor pressure of the *Sample* at 21° by means of a suitable pressure gauge.

Acceptance criteria: 820–875 kPa absolute (119–127 psia)

ASSAY

Change to read:

PROCEDURE

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: GC

Detector: Thermal conductivity

Column: 6-m × 3-mm aluminum; packed with 10 weight percent of liquid phase G30 on support S1D_{MS} (NF31)

Column temperature: 33°

Carrier gas: Helium

Flow rate: 50 mL/min

Injection volume: 2 μL

System suitability

Sample: Propane

Suitability requirements: The peak responses for Propane from duplicate determinations agree within 1%.

Analysis: Connect one Propane cylinder to the chromatograph through a suitable sampling valve and a flow control valve downstream from the sampling valve. Flush the liquid specimen through the sampling valve, taking care to avoid entrapment of gas or air in the sampling valve. Calculate the percentage purity by dividing 100 times the propane response by the sum of all of the responses.

Acceptance criteria: NLT 98.0%

SPECIFIC TESTS

HIGH-BOILING RESIDUES

Sample: Use the *Sample* from *Identification* test B.

Analysis: Prepare a cooling coil from copper tubing (about 6-mm outside diameter × about 6.1-m long) to fit into a vacuum-jacketed flask. Immerse the cooling coil in a mixture of dry ice and acetone in a vacuum-jacketed flask, and connect one end of the tubing to the *Sample*. Carefully open the sample cylinder valve, flush the cooling coil with about 50 mL of the *Sample*, and discard this portion of liquefied sample. Continue delivering liquefied sample from the cooling coil, and collect it in a previously chilled 1000-mL sedimentation cone until the cone is filled to the 1000-mL mark. Allow the sample to evaporate, using a warm water bath maintained at about 40° to reduce evaporating time. When all of the liquid has evaporated, rinse the sedimentation cone with two 50-mL portions of pentane, and combine the rinsings in a tared 150-mL evaporating dish. Transfer 100 mL of the pentane solvent to a second tared 150-mL evaporating dish, place both evaporating dishes on a water bath, evaporate to dryness, and heat the dishes in an oven at 100° for 60 min. Cool the dishes in a desiccator, and weigh. Repeat the heating for 15-min periods until successive weighings are within 0.1 mg, and calculate the weight of the residue obtained from the *Sample* as the difference between the weights of the residues in the two evaporating dishes.

Acceptance criteria: NMT 5 μg/mL

ACIDITY OF RESIDUE

Sample solution: Add 10 mL of water to the residue obtained in the test for *High-Boiling Residues*, mix by swirling for 30 s, add 2 drops of methyl orange TS, insert the stopper in the tube, and shake vigorously.

Acceptance criteria: No pink or red color appears in the aqueous layer.

LIMIT OF SULFUR COMPOUNDS

Analysis: Carefully open the container valve to produce a moderate flow of gas. Do not direct the gas stream toward the face, but deflect a portion of the stream toward the nose.

Acceptance criteria: The odor is free from the characteristic odor of sulfur compounds.

WATER DETERMINATION ⟨921⟩

Sample: 100 g of the *Sample* from *Identification* test B

Analysis: Proceed as directed in the chapter with the following modifications. (a) Provide the closed-system titrating vessel with an opening through which passes a coarse-porosity gas dispersion tube connected to a sampling cylinder. (b) Dilute the *Reagent* with anhydrous methanol to give a water equivalence factor of 0.2–1.0 mg/mL; age this diluted solution for NLT 16 h before standardization. (c) Introduce the *Sample* into the titration vessel through the gas dispersion tube at a rate of about 100 mL/min; if necessary, heat the sample cylinder gently to maintain this flow rate.

Acceptance criteria: NMT 0.001%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight cylinders, and prevent exposure to excessive heat.

Add the following:

Propanediol



C₃H₈O₂ 76.09

1,3-Propanediol;
1,3-Dihydroxypropane;
Propane, 1-3-diol;
Trimethylene glycol [504-63-2].

DEFINITION

Propanediol contains NLT 99.7% of 1,3-propanediol (C₃H₈O₂). It may be of vegetable, other natural source, or synthetic origin.

IDENTIFICATION

A. INFRARED ABSORPTION ⟨197F⟩

• **B.** The retention time of the major peak of the *Sample* solution corresponds to the 1,3-propanediol peak of the *System suitability* solution, as obtained in the *Assay*.

ASSAY

PROCEDURE

System suitability solution: Mix quantities of USP Propylene Glycol RS and USP 1,3-Propanediol RS to obtain a solution containing about 5% propylene glycol and 95% propanediol.

Sample solution: Propanediol (neat)

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.25-mm × 30-m capillary column; bonded with a 0.25-μm layer of phase G16

Temperatures

Detector: 250°

Injection port: 250°

Column: See Table 1.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	15	200	—
200	40	250	17

Carrier gas: Helium

Flow rate: 1.1 mL/min

Injection volume: 0.2 µL

Split type: Split ratio of 18:1

System suitabilitySample: *System suitability solution*

[NOTE—The relative retention times for propylene glycol and propanediol are 0.7 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the peaks due to propylene glycol and propanediol

AnalysisSample: *Sample solution*

Calculate the percentage of propanediol in the portion of sample taken:

$$\text{Result} = (r_U/r_T) \times 100$$

 r_U = peak response for propanediol in the *Sample solution* r_T = sum of all peak responses in the *Sample solution*

Acceptance criteria: NLT 99.7%

IMPURITIES**• LIMIT OF RELATED GLYCOL SUBSTANCES**

System suitability solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

AnalysisSample: *Sample solution*

Calculate the percentage of each individual impurity in the portion of Propanediol taken:

$$\text{Result} = (r_U/r_T) \times 100$$

 r_U = peak response of each individual impurity in the *Sample solution* r_T = sum of all peak responses in the *Sample solution***Acceptance criteria**

Each individual impurity: NMT 0.1%

Total impurities: NMT 0.3%

• LIMIT OF ALDEHYDES**Formaldehyde methanol solution:**¹ A solution containing 37% (w/w) of formaldehyde and 10%–15% (w/w) of methanol in water**Phenolphthalein solution:** Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL.**Quantification of Formaldehyde methanol solution:**To 2.0 g of *Formaldehyde methanol solution*, add 100 mL of a freshly prepared 100 mg/mL solution of sodium sulfite in carbon-dioxide free water. Add 0.1 mL of *Phenolphthalein solution*, and titrate with 0.5 N sulfuric acid until the color changes from pink to colorless. Carry out a blank titration.¹ Formaldehyde TS can be used for *Formaldehyde methanol solution*.Calculate the percentage content of formaldehyde in *Formaldehyde methanol solution* using the following expression:

$$\text{Result } (P_{\text{HCHO}}) = \{(V_S - V_B) \times N \times M_W \times F/W\} \times 100$$

 V_S = volume of 0.5 N sulfuric acid used in the assay (mL) V_B = volume of 0.5 N sulfuric acid used in the blank (mL) N = normality of the titrant (mEq/mL) M_W = milliequivalent weight of formaldehyde, 30.03 mg/mEq F = unit conversion factor, 10^{-3} g/mg W = weight of sample (g)**Standard stock solution:** 1.2 µg/mL of *Formaldehyde methanol solution* in carbon-dioxide free water, prepared from appropriately diluting *Formaldehyde methanol solution* in carbon-dioxide free water**Standard solutions:** Introduce into 50-mL volumetric flasks 1.0-, 3.0-, 5.0-, 10.0-, 15.0-, and 25.0-mL of *Standard stock solution*, respectively. Calculate the content of formaldehyde, in µg, in the *Standard solutions* using the following expression. Proceed as directed in the *Analysis* below.

$$\text{Result (content of formaldehyde)} = V \times C \times P_{\text{HCHO}} \times 0.01$$

 V = volume of the *Standard stock solution* added into the *Standard solution* (mL) C = concentration of *Formaldehyde methanol solution* in the *Standard stock solution* (µg/mL) P_{HCHO} = percentage content of formaldehyde in *Formaldehyde methanol solution*, as determined above**Sample solution:** Introduce 5.0 mL of 0.2 g/mL of propanediol in carbon-dioxide free water into a 50-mL volumetric flask. Proceed as directed in the *Analysis* below.**Blank solution:** Prepare in the same manner as for the *Standard solutions* but omitting the *Standard stock solution*.**Instrumental conditions**(See *Spectrophotometry and Light-Scattering* (851).)**Mode:** Vis spectrophotometry**Analytical wavelength:** 655 nm**Analysis****Samples:** *Blank solution*, *Standard solutions*, and *Sample solution*To each flask of the *Blank solution*, *Standard solutions*, and *Sample solution* add 2 mL of a freshly prepared 5 mg/mL solution of methylbenzothiazolone hydrazone hydrochloride adjusted with 0.02 N sodium hydroxide to a pH of 4.0. Allow the solutions to stand for 30 min. Add 5 mL of a freshly prepared 7 mg/mL solution of ferric chloride. Cap and swirl the flasks. Allow to stand for 5 min. Add methanol to each flask, and dilute with methanol to 50.0 mL. Mix thoroughly, then allow to stand for 1 min.Measure the absorbance of the solutions using the treated *Blank solution* as compensation liquid.Plot the absorbance of the treated *Standard solution* versus the content of formaldehyde, in µg, in the *Standard solution*. Obtain the content of formaldehyde W_{HCHO} , in µg, in the treated *Sample solution* based on the calibration curve.

Calculate the content of aldehydes expressed as formaldehyde (HCHO) in the portion of Propanediol taken:

$$\text{Result} = W_{\text{HCHO}}/(C \times V)$$

 W_{HCHO} = content of formaldehyde in the treated *Sample solution*, determined from the calibration curve (µg)

- C** = concentration of Propanediol in the *Sample solution* (g/mL)
V = volume of the *Sample solution* in the analysis (mL)

Acceptance criteria: NMT 20 µg/g, expressed as HCHO.

SPECIFIC TESTS

• ACIDITY

Sample: 50 mL of Propanediol

Phenolphthalein solution: Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL.

Titrimetric system

(See *Titrimetry* <541>)

Mode: Direct titration

Titrant: 0.01 N sodium hydroxide VS

Endpoint detection: Visual

Analysis: To 50 mL of water, add 1 mL of *Phenolphthalein solution*, then add *Titrant* until the solution remains pink for 30 s. Add the *Sample*, and titrate with *Titrant* until the color turns back to pink and remains for more than 30 s.

Calculate the acidity, as acetic acid (CH₃COOH):

$$\text{Result} = (V_T \times N \times W_{\text{MEq}}) / V_S$$

V_T = *Titrant volume* (mL)

N = *Titrant normality* (mEq/mL)

W_{MEq} = milliequivalent weight of acetic acid, 60.05 mg/mEq

V_S = volume of Propanediol in the *Sample* (mL)

Acceptance criteria: NMT 0.1 mg/mL, calculated as acetic acid (CH₃COOH)

• WATER DETERMINATION, Method 1c <921>: NMT 0.1%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Do not store above 50°. Protect from moisture.

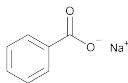
• **LABELING:** Label it to indicate whether Propanediol is derived from vegetable, other natural source, or synthetic origin.

• USP REFERENCE STANDARDS <11>

USP 1,3-Propanediol RS

USP Propylene Glycol RS ■1S (NF31)

Sodium Benzoate



C₇H₅NaO₂

Benzoic acid, sodium salt;

Sodium benzoate [532-32-1].

144.10

DEFINITION

Change to read:

Sodium Benzoate contains NLT 99.0% and NMT

■101.0% ■1S (NF31) of sodium benzoate (C₇H₅NaO₂), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• A. ■INFRARED ABSORPTION <197K>

Sample: Undried sample

Acceptance criteria: Meets the requirements ■1S (NF31)

• B. IDENTIFICATION TESTS—GENERAL, Sodium <191>: Meets the requirements

Change to read:

• C. ■The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■1S (NF31)

ASSAY

Change to read:

• PROCEDURE

■**Solution A:** Adjust a 20-mM solution of monobasic potassium phosphate with phosphoric acid to a pH of 2.5.

Mobile phase: *Solution A* and acetonitrile (70:30)

Diluent: Water and acetonitrile (50:50)

System suitability solution: 0.1 mg/mL of USP Salicylic Acid RS and 0.1 mg/mL of USP Benzoic Acid RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Benzoic Acid RS in *Diluent*

Sample solution: 0.1 mg/mL of Sodium Benzoate in *Diluent*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 25°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for benzoic acid and salicylic acid are approximately 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 3.0 between benzoic acid and salicylic acid, *System suitability solution*

Relative standard deviation: NMT 0.5% for benzoic acid, *Standard solution*

Tailing factor: NMT 2.0 for benzoic acid, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sodium benzoate

(C₇H₅NaO₂) in the portion of Sodium Benzoate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of benzoic acid from the *Sample solution*

r_S = peak area of benzoic acid from the *Standard solution*

C_S = concentration of benzoic acid in the *Standard solution*, corrected for purity (mg/mL)

C_U = concentration of Sodium Benzoate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of sodium benzoate, 144.10

M_{r2} = molecular weight of benzoic acid, 122.12

Acceptance criteria: 99.0%–101.0% on the anhydrous basis ■1S (NF31)

IMPURITIES• **HEAVY METALS** <231>

Test preparation: 4.0 g in 40 mL of water

Analysis: To the *Test preparation* add, dropwise with vigorous stirring, 10 mL of 3 N hydrochloric acid, and filter. Use 25 mL of the filtrate.

Acceptance criteria: NMT 10 µg/g

SPECIFIC TESTS• **WATER DETERMINATION, Method I** <921>: NMT 1.5%• **ALKALINITY**

Sample solution: 2 g in 20 mL of hot water

Analysis: To the *Sample solution* add 2 drops of phenolphthalein TS.

Acceptance criteria: The pink color produced, if any, is discharged by the addition of 0.20 mL of 0.10 N sulfuric acid.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.

Change to read:• **USP REFERENCE STANDARDS** <11>

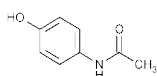
■ USP Benzoic Acid RS

USP Salicylic Acid RS ■ 1S (NF31)

USP Sodium Benzoate RS

Official Monographs for USP 36

Acetaminophen



$C_8H_9NO_2$ 151.16
Acetamide, *N*-(4-hydroxyphenyl)-;
4'-Hydroxyacetanilide [103-90-2].

DEFINITION

Change to read:

Acetaminophen contains NLT 98.0% and NMT
102.0% \blacksquare _{1S} (USP36) of acetaminophen ($C_8H_9NO_2$), calculated
on the \blacksquare dried basis. \blacksquare _{1S} (USP36)

IDENTIFICATION

• A. INFRARED ABSORPTION <197K>

Change to read:

- **B.** \blacksquare The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. \blacksquare _{1S} (USP36)

Delete the following:

• C. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST <201>

Sample solution: 1 mg/mL in methanol
Developing solvent system: Methylene chloride and methanol (4:1)

Acceptance criteria: Meets the requirements of the test. \blacksquare _{1S} (USP36)

ASSAY

Change to read:

• PROCEDURE

\blacksquare Use low-actinic glassware for preparation of the *Sample solution*.

Solution A: 1.7 g/L of monobasic potassium phosphate and 1.8 g/L of dibasic sodium phosphate, anhydrous

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	99	1
3.0	99	1
7.0	19	81

Table 1 (Continued)

Time (min)	Solution A (%)	Solution B (%)
7.1	99	1
10.0	99	1

Standard solution: 0.1 mg/mL of USP Acetaminophen RS in methanol

Sample solution: 0.1 mg/mL of Acetaminophen in methanol

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: 230

Column: 4.6-mm \times 10-cm; 3.5- μ m packing L7

Column temperature: 35°

Flow rate: 1.0 mL/min

Injection volume: 5 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of acetaminophen ($C_8H_9NO_2$) in the portion of Acetaminophen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Acetaminophen RS in the *Standard solution* (mg/mL)

C_U = concentration of Acetaminophen in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis. \blacksquare _{1S} (USP36)

IMPURITIES

• RESIDUE ON IGNITION <281>: NMT 0.1%

Delete the following:

• CHLORIDE AND SULFATE, Chloride <221>

Sample solution: Shake 1.0 g of Acetaminophen with 25 mL of water, filter, and add 1 mL of 2 N nitric acid and 1 mL of silver nitrate TS.

Acceptance criteria: The filtrate shows no more chloride than corresponds to 0.20 mL of 0.020 N hydrochloric acid (0.014%). \blacksquare _{1S} (USP36)

Delete the following:

• CHLORIDE AND SULFATE, Sulfate <221>

Sample solution: Shake 1.0 g of Acetaminophen with 25 mL of water, filter, and add 2 mL of 1 N acetic acid, then add 2 mL of barium chloride TS.

Acceptance criteria: The mixture shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (0.02%). ■1S (USP36)

Delete the following:

• **SULFIDE**

Sample: 2.5 g

Analysis: Place the *Sample* in a 50-mL beaker. Add 5 mL of alcohol and 1 mL of 3 N hydrochloric acid. Moisten a piece of lead acetate test paper with water, and fix to the underside of a watch glass. Cover the beaker with the watch glass so that part of the lead acetate paper hangs down near the pouring spout of the beaker. Heat the contents of the beaker on a hot plate just to boiling.

Acceptance criteria: No coloration or spotting of the test paper occurs. ■1S (USP36)

• **HEAVY METALS, Method II (231):** NMT 10 ppm

Change to read:

• **LIMIT OF FREE *p*-AMINOPHENOL**

■**Solution A, Solution B, Mobile phase, and Chromatographic system:** Proceed as directed in the Assay.

Standard solution: 1.25 µg/mL of USP 4-Aminophenol RS in methanol

Sample solution: 25 mg/mL of Acetaminophen in methanol

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for *p*-aminophenol and acetaminophen are 0.6 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 4-aminophenol (C₆H₇NO) in the portion of Acetaminophen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of 4-aminophenol from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP 4-Aminophenol RS in the *Standard solution* (µg/mL)

C_U = concentration of Acetaminophen in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 0.005% ■1S (USP36)

Change to read:

• **ORGANIC IMPURITIES**

■**Solution A:** Methanol, water, acetic acid (50:950:1)

Solution B: Methanol, water, acetic acid (500:500:1)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	82	18
8	82	18
53	0	100
58	0	100
59	82	18
73	82	18

Diluent: Methanol

Standard solution: 1.25 µg/mL of USP Acetaminophen Related Compound D RS and 0.25 µg/mL of USP Acetaminophen Related Compound J RS in *Diluent*

System suitability solution: 20 µg/mL of USP Acetaminophen RS, and 80 µg/mL each of USP Acetaminophen Related Compound B RS and USP Acetaminophen Related Compound C RS in *Diluent*

Sample solution: 25 mg/mL of Acetaminophen in *Diluent*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 0.9 mL/min

Column temperature: 40°

Injection volume: 5 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—See *Table 3* for relative retention time values.]

Suitability requirements

Tailing factor: NMT 2.0 for acetaminophen related compound D, *Standard solution*

Resolution: NLT 2.0 between acetaminophen and acetaminophen related compound B, and NLT 1.5 between acetaminophen related compound B and acetaminophen related compound C, *System suitability solution*

Relative standard deviation: NMT 5.0% for acetaminophen related compound D, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of acetaminophen related compound J in the portion of Acetaminophen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of acetaminophen related compound J from the *Sample solution*

r_S = peak response of acetaminophen related compound J from the *Standard solution*

C_S = concentration of USP Acetaminophen Related Compound J RS in the *Standard solution* (µg/mL)

C_U = concentration of Acetaminophen in the *Sample solution* (µg/mL)

Calculate the percentage of acetaminophen related compounds B, C, and D and any unspecified impurity in the portion of Acetaminophen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 1/F \times 100$$

r_U = peak response of each specified or unspecified impurity from the *Sample solution*

r_S = peak response of acetaminophen related compound D from the *Standard solution*

C_S = concentration of USP Acetaminophen Related Compound D RS in the *Standard solution* (µg/mL)

C_U = concentration of Acetaminophen in the *Sample solution* (µg/mL)

F = relative response factor for each impurity shown in *Table 3*

Acceptance criteria: See Table 3.

Table 3

Name	Relative Retention Time ^a	Relative Response Factor	Acceptance Criteria, NMT (%)
Acetaminophen	0.43	—	—
Acetaminophen related compound B ^a	0.67	1.0	0.05
Acetaminophen related compound C ^b	0.71	1.0	0.05
Acetaminophen related compound D ^c	1.0	1.0	0.05
Acetaminophen related compound J ^d	1.73	—	0.001
Individual unspecified impurity	—	—	0.05
Total impurities	—	—	0.1

^a *N*-(4-Hydroxyphenyl)propanamide.

^b *N*-(2-Hydroxyphenyl)acetamide.

^c *N*-Phenylacetamide.

^d *N*-(4-Chlorophenyl)acetamide (*p*-chloroacetanilide).

* Calculated relative to acetaminophen related compound D.

■1S (USP36)

SPECIFIC TESTS

Delete the following:

• MELTING RANGE OR TEMPERATURE (741):

168°–172° ■1S (USP36)

Delete the following:

• WATER DETERMINATION, Method I (921): NMT

0.5% ■1S (USP36)

Add the following:

• LOSS ON DRYING (731)

Analysis: Dry at 105° to constant weight.

Acceptance criteria: NMT 0.5% ■1S (USP36)

Delete the following:

• READILY CARBONIZABLE SUBSTANCES TEST (271):

Dissolve 0.50 g in 5 mL of sulfuric acid: the solution has no more color than Matching Fluid A. ■1S (USP36)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at room temperature. Protect from moisture and heat.

Change to read:

• USP REFERENCE STANDARDS (11)

USP Acetaminophen RS

■ USP Acetaminophen Related Compound B RS

N-(4-Hydroxyphenyl)propanamide.

C₉H₁₁NO₂ 165.19

USP Acetaminophen Related Compound C RS

N-(2-Hydroxyphenyl)acetamide.

C₈H₉NO₂ 151.16

USP Acetaminophen Related Compound D RS

N-Phenylacetamide.

C₈H₉NO 135.17

USP Acetaminophen Related Compound J RS

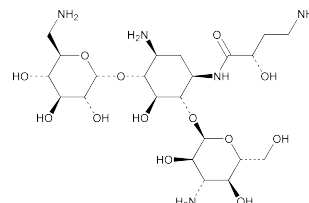
N-(4-Chlorophenyl)acetamide (*p*-chloroacetanilide).

C₈H₈ClNO 169.61

USP 4-Aminophenol RS

C₆H₇NO 109.13 ■1S (USP36)

Amikacin



C₂₂H₄₃N₅O₁₃ 585.60

D-Streptamine, O-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[6-amino-6-deoxy-α-D-glucopyranosyl(1→4)]-N¹-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)-; O-3-Amino-3-deoxy-α-D-glucopyranosyl(1→4)-O-[6-amino-6-deoxy-α-D-glucopyranosyl(1→6)]-N³-(4-amino-2-hydroxybutyl)-2-deoxy-L-streptamine [37517-28-5].

DEFINITION

Amikacin has a potency of NLT 900 μg/mg of C₂₂H₄₃N₅O₁₃, calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- **A. ■INFRARED ABSORPTION (197K)** ■1S (USP36)
- **B.** The retention time of the peak for amikacin of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

Change to read:

• PROCEDURE

Mobile phase: 0.115 N sodium hydroxide

System suitability solution: 0.02 mg/mL of USP

Amikacin RS and 0.008 mg/mL of USP Kanamycin Sulfate RS in water

Standard solution: 0.02 mg/mL of USP Amikacin RS in water

Sample solution: 0.02 mg/mL of Amikacin in water

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: Electrochemical

Detector mode: Integrated amperometric mode

Electrodes

Working: Gold

Reference: Silver–silver chloride

Detector settings: See Table 1.

■1S (USP36)

Table 1

Potential		Time (ms)
No.	V	
E ₁	0.04	200
E ₂	0.8	190
E ₃	−0.8	190

Columns**Guard:** Packing L47**Analytical:** 4-mm × 25-cm; \blacksquare 10- μ m \blacksquare 1S (USP36) packing L47**Flow rate:** 0.5 mL/min**Injection size:** 20 μ L**System suitability****Samples:** *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for kanamycin and amikacin are 0.8 and 1.0, respectively.]

Suitability requirements**Resolution:** NLT 3 between kanamycin and amikacin, *System suitability solution***Tailing factor:** NMT 2, *Standard solution***Relative standard deviation:** NMT 3%, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the quantity, in μ g, of amikacin ($C_{22}H_{43}N_5O_{13}$) in each mg of Amikacin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F$$

 r_U = peak area from the *Sample solution* r_S = peak area from the *Standard solution* C_S = concentration of USP Amikacin RS in the *Standard solution* (mg/mL) C_U = concentration of the *Sample solution* (mg/mL) P = potency of amikacin in USP Amikacin RS (mg/mg) F = conversion factor, 1000 μ g/mg**Acceptance criteria:** NLT 900 μ g/mg on the anhydrous basis**IMPURITIES**

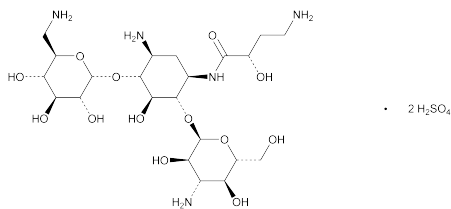
- RESIDUE ON IGNITION** (281): NMT 1.0%, the charred residue being moistened with 2 mL of nitric acid and 5 drops of sulfuric acid

SPECIFIC TESTS

- OPTICAL ROTATION**, *Specific Rotation* (781S)
Sample solution: 20 mg/mL in water
Acceptance criteria: +97° to +105°
- CRYSTALLINITY** (695): Meets the requirements
- PH** (791)
Sample solution: 10 mg/mL in water
Acceptance criteria: 9.5–11.5
- WATER DETERMINATION**, *Method I* (921): NMT 8.5%

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in tight containers.
- USP REFERENCE STANDARDS** (11)
 USP Amikacin RS
 USP Kanamycin Sulfate RS

Amikacin Sulfate**Change to read:** \blacksquare $C_{22}H_{43}N_5O_{13} \cdot 1.8H_2SO_4$ \blacksquare 1S (USP36) 762.15 $C_{22}H_{43}N_5O_{13} \cdot 2H_2SO_4$ 781.76D-Streptamine, O-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 6)-O-[6-amino-6-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)]-N¹-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)-, sulfate (1:2 or 1:1.8) (salt);O-3-Amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-O-[6-amino-6-deoxy- α -D-glucopyranosyl-(1 \rightarrow 6)]-N³-(4-amino-L-2-hydroxybutyl)-2-deoxy-L-streptamine sulfate (1:2 or 1:1.8) [39831-55-5].**DEFINITION**Amikacin Sulfate having a molar ratio of amikacin to H_2SO_4 of 1:2 contains the equivalent of NLT 674 μ g/mg and NMT 786 μ g/mg of $C_{22}H_{43}N_5O_{13}$, calculated on the dried basis; Amikacin Sulfate having a molar ratio of amikacin to H_2SO_4 of 1:1.8 contains the equivalent of NLT 691 μ g/mg and NMT 806 μ g/mg of $C_{22}H_{43}N_5O_{13}$, calculated on the dried basis.**IDENTIFICATION****Change to read:**

- A. INFRARED ABSORPTION** (197K): The IR absorption spectrum conforms to that of USP Amikacin Sulfate RS, similarly obtained. \blacksquare 1S (USP36)
- B.** The retention time of the peak for amikacin of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

Add the following:

- C. IDENTIFICATION TESTS—GENERAL**, *Sulfate* (191): Meets the requirements \blacksquare 1S (USP36)

ASSAY**Change to read:**

- PROCEDURE**
Mobile phase: 0.115 N sodium hydroxide
System suitability solution: 0.02 mg/mL of USP Amikacin RS and 0.008 mg/mL of USP Kanamycin Sulfate RS in water
Standard solution: 0.02 mg/mL of USP Amikacin RS in water
Sample solution: Equivalent to 0.02 mg/mL of amikacin, from Amikacin Sulfate, in water
Chromatographic system
 (See *Chromatography* (621), *System Suitability*).
Mode: LC
Detector: Electrochemical
Detector mode: Integrated amperometric mode
Electrodes
Working: Gold
Reference: Silver–silver chloride
Detector settings: See *Table 1*.
 \blacksquare 1S (USP36)

Table 1

Potential		Time (ms)
No.	V	
E ₁	0.04	200
E ₂	0.8	190
E ₃	−0.8	190

Columns**Guard:** Packing L47**Analytical:** 4-mm × 25-cm; \blacksquare 10- μ m \blacksquare 1S (USP36) packing L47

Flow rate: 0.5 mL/min

Injection size: 20 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for kanamycin and amikacin are 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3 between kanamycin and amikacin, *System suitability solution*

Tailing factor: NMT 2, *Standard solution*

Relative standard deviation: NMT 3%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in μ g, of amikacin ($C_{22}H_{43}N_5O_{13}$) in each mg of Amikacin Sulfate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Amikacin RS in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

P = potency of amikacin in USP Amikacin RS (mg/mg)

F = conversion factor, 1000 μ g/mg

Acceptance criteria: See Table 2.

Table 2

Ratio of Amikacin:H ₂ SO ₄	Acceptance Criteria (μ g/mg) ^a
1:2	674–786
1:1.8	691–806

^a Calculated on the dried basis.

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 1.0%, the charred residue being moistened with 2 mL of nitric acid and 5 drops of sulfuric acid

SPECIFIC TESTS

- **OPTICAL ROTATION**, *Specific Rotation* (781)
Sample solution: 20 mg/mL in water
Acceptance criteria: +76° to +84°
- **CRYSTALLINITY** (695): Meets the requirements
- **pH** (791)
Sample solution: 10 mg/mL in water
Acceptance criteria: See Table 3.

Table 3

Ratio of Amikacin:H ₂ SO ₄	Acceptance Criteria
1:2	2.0–4.0
1:1.8	6.0–7.3

- **LOSS ON DRYING** (731): Dry 100 mg in a vacuum at a pressure not exceeding 5 mm of mercury at 110° for 3 h; it loses NMT 13.0% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** Label it to indicate whether its molar ratio of amikacin to H₂SO₄ is 1:2 or 1:1.8.

Change to read:

- **USP REFERENCE STANDARDS** (11)
 USP Amikacin RS
 ■ USP Amikacin Sulfate RS^{■1S} (USP36)
 USP Kanamycin Sulfate RS

Amikacin Sulfate Injection

DEFINITION

Amikacin Sulfate Injection is a sterile solution of Amikacin Sulfate in Water for Injection, or of Amikacin in Water for Injection prepared with the aid of Sulfuric Acid. It contains NLT 90.0% and NMT 120.0% of the labeled amount of amikacin ($C_{22}H_{43}N_5O_{13}$).

IDENTIFICATION

Delete the following:

■ A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST (201)

Standard solution: 6 mg/mL

Sample solution: 6 mg/mL

Solution A: *Sample solution* and the *Standard solution* (1:1)

Application volume: 3 μ L

Developing solvent system: Methanol, chloroform, and ammonium hydroxide (12:5:7)

Spray reagent: 10 mg/mL of ninhydrin in a mixture of butyl alcohol and pyridine (100:1)

Analysis

Samples: *Standard solution*, *Sample solution*, and *Solution A*

Proceed as directed in the chapter, except to develop the chromatogram by continuous flow for 5.5 h. Remove the plate from the chamber, allow the solvent to evaporate, and heat the plate at 110° for 15 min. Spray the plate with *Spray reagent*, and immediately locate the spots.

Acceptance criteria: Amikacin appears as a pink spot, and the spots obtained from the *Sample solution* and the *Solution A* correspond in distance from the origin to that obtained from the *Standard solution*.^{■1S} (USP36)

Change to read:

- **■A.■1S** (USP36) The retention time of the peak for amikacin of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• PROCEDURE

Mobile phase: 0.115 N sodium hydroxide

System suitability solution: 0.02 mg/mL of USP Amikacin RS and 0.008 mg/mL of USP Kanamycin Sulfate RS in water

Standard solution: 0.02 mg/mL of USP Amikacin RS in water

Sample solution: 0.02 mg/mL of amikacin, from the Injection in water

Chromatographic system(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** Electrochemical**Detector mode:** Integrated amperometric mode**Electrodes****Working:** Gold**Reference:** Silver–silver chloride**Detector settings:** See *Table 1*.

■1S (USP36)

Table 1

Potential		Time (ms)
No.	V	
E ₁	0.04	200
E ₂	0.8	190
E ₃	–0.8	190

Columns**Guard:** Packing L47**Analytical:** 4-mm × 25-cm; ■10-μm■1S (USP36) packing L47**Flow rate:** 0.5 mL/min**Injection size:** 20 μL**System suitability****Samples:** *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for kanamycin and amikacin are 0.8 and 1.0, respectively.]

Suitability requirements**Resolution:** NLT 3 between kanamycin and amikacin, *System suitability solution***Tailing factor:** NMT 2, *Standard solution***Relative standard deviation:** NMT 3%, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of amikacin (C₂₂H₄₃N₅O₁₃) in each mL of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

 r_U = peak area from the *Sample solution* r_S = peak area from the *Standard solution* C_S = concentration of USP Amikacin RS in the *Standard solution* (mg/mL) C_U = nominal concentration of amikacin in the *Sample solution* P = potency of amikacin in USP Amikacin RS (mg/mg)**Acceptance criteria:** 90.0%–120.0%**SPECIFIC TESTS**• **pH** <791>: 3.5–5.5• **PARTICULATE MATTER IN INJECTIONS** <788>: Meets the requirements for small-volume injections• **BACTERIAL ENDOTOXINS TEST** <85>: NMT 0.33 USP Endotoxin Unit/mg of amikacin• **OTHER REQUIREMENTS:** Meets the requirements under *Injections* <1>**ADDITIONAL REQUIREMENTS**• **PACKAGING AND STORAGE:** Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass.• **USP REFERENCE STANDARDS** <11>

USP Amikacin RS

USP Endotoxin RS

USP Kanamycin Sulfate RS

Amiloride Hydrochloride Tablets**DEFINITION**Amiloride Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of amiloride hydrochloride (C₆H₈ClN₇O · HCl).**IDENTIFICATION**• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.• **B.** **Standard solution:** 0.2 mg/mL of USP Amiloride Hydrochloride RS in methanol**Sample solution:** Prepare from finely ground Tablets, equivalent to 0.2 mg/mL of amiloride hydrochloride in methanol. Filter the solution.**Chromatographic system**(See *Chromatography* <621>, *Thin-Layer Chromatography*.)**Mode:** TLC**Adsorbent:** 0.25-mm layer of chromatographic silica gel mixture**Developing solvent system:** Tetrahydrofuran and 3 N ammonium hydroxide (88:12)**Application volume:** 10 μL**Analysis****Samples:** *Standard solution* and *Sample solution*

Develop the plate until the solvent is about three-fourths of the length of the plate from the origin. Remove the plate from the developing chamber, air-dry, and examine under short-wavelength UV light.

Acceptance criteria: The R_f value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.**ASSAY**• **PROCEDURE****Buffer:** Dissolve 136 g of monobasic potassium phosphate in 800 mL of water. Adjust with phosphoric acid to a pH of 3.0. Dilute with water to 1000 mL.**Mobile phase:** Methanol, water, and *Buffer* (25:71:4)**Standard stock solution:** 1.0 mg/mL of USP Amiloride Hydrochloride RS in methanol**Standard solution:** 0.1 mg/mL of USP Amiloride Hydrochloride RS from *Standard stock solution*, prepared as follows. Transfer 5.0 mL of the *Standard stock solution* to a 50-mL volumetric flask. Add 10.0 mL of methanol, 2.0 mL of 0.1 N hydrochloric acid, and dilute with water to volume.**Sample solution:** Transfer an amount equivalent to 5 mg of amiloride hydrochloride, from NLT 20 finely powdered Tablets, to a 50-mL volumetric flask containing 15.0 mL of methanol and 2.0 mL of 0.1 N hydrochloric acid. Sonicate for 10 min, dilute with water to volume, sonicate for an additional 10 min, and filter.**Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 286 nm**Column:** 3.9-mm × 30-cm; packing L1**Flow rate:** 1 mL/min**Injection volume:** 10 μL**System suitability****Sample:** *Standard solution***Suitability requirements****Tailing factor:** NMT 2.0**Relative standard deviation:** NMT 2.0%**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of the labeled amount of amiloride hydrochloride (C₆H₈ClN₇O · HCl) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- r_U = peak response of amiloride from the *Sample solution*
 r_S = peak response of amiloride from the *Standard solution*
 C_S = concentration of USP Amiloride Hydrochloride RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of amiloride hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• DISSOLUTION <711>

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Instrumental conditions

Mode: UV

Analytical wavelength: 363 nm

Standard solution: USP Amiloride Hydrochloride RS of known concentration in *Medium*. [NOTE—An amount of methanol not to exceed 2% of the total volume of the *Standard solution* may be used to dissolve the amiloride hydrochloride.]

Sample solution: Sample per *Dissolution* <711>. Dilute with *Medium* as necessary.

Analysis

Samples: *Standard solution* and *Sample solution*

Tolerances: NLT 80% (Q) of the labeled amount of amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl$) is dissolved.

• UNIFORMITY OF DOSAGE UNITS <905>

Procedure for content uniformity

Standard solution: 10 µg/mL of USP Amiloride Hydrochloride RS in 0.1 N hydrochloric acid

Sample solution: 10 µg/mL of amiloride hydrochloride prepared as follows. Transfer one finely powdered Tablet to a 100-mL volumetric flask, add 60 mL of 0.1 N hydrochloric acid, and shake by mechanical means for 30 min. Dilute with 0.1 N hydrochloric acid to volume, and centrifuge a portion of the mixture. Dilute a portion of the clear supernatant to obtain the required concentration.

Instrumental conditions

Mode: UV

Analytical wavelength: 363 nm

Blank: 0.1 N hydrochloric acid

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amiloride hydrochloride ($C_6H_8ClN_7O \cdot HCl$) in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of amiloride hydrochloride in the *Sample solution*

A_S = absorbance of amiloride hydrochloride in the *Standard solution*

C_S = concentration of USP Amiloride Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of amiloride hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: Meet the requirements

IMPURITIES

Add the following:

• ORGANIC IMPURITIES

Diluent: Methanol, 1 N hydrochloric acid, and water (40:4:56)

Buffer: 0.9 g/L of sodium 1-hexanesulfonate in water. Initially add water to about 90% of the volume of the flask, adjust with diluted phosphoric acid to a pH of 3.0 ± 0.1, and dilute with water to volume.

Mobile phase: Acetonitrile and *Buffer* (10:90)

Standard solution: 0.01 mg/mL of USP Amiloride Hydrochloride RS in *Diluent*

Sample solution: Nominally equivalent to 2 mg/mL of amiloride hydrochloride in *Diluent* from NLT 20 powdered Tablets. Initially add methanol to fill about 40% of the volume of the flask and 1 N hydrochloric acid to about 4% of the volume of the flask. Sonicate for 10 min, dilute with water to volume, and sonicate for another 10 min. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 350 nm

Column: 4.6-mm × 15-cm; 4-µm packing L1

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of amiloride from the *Standard solution*

C_S = concentration of USP Amiloride Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of amiloride hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See Table 1.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Chloropyrazine acid ^{a,e}	0.15	—
Chloropyrazine methyl carboxylate ^{b,e}	0.48	—
Chloropyrazine carboxamide ^{c,e}	0.56	—
Amiloride	1.00	—
Any other unknown impurity	—	0.5
Total impurities ^d	—	2.0

^a 3,5,-Diamin-6-chloropyrazine carboxylic acid.

^b 3,5,-Diamin-6-chloropyrazine-2-carboxylate.

^c N-Amididine-3-amino-5-hydroxy-6-chloropyrazine-2-carboxamide hydrochloride.

^d Total impurities is the sum of all the impurities including process-related. Disregard peaks less than 0.05%.

^e Process-related impurity, controlled in the drug substance.

■1S (USP36)

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers.

• **USP REFERENCE STANDARDS <11>**
USP Amiloride Hydrochloride RS

Add the following:**•Amlodipine and Benazepril Hydrochloride Capsules****DEFINITION**

Amlodipine and Benazepril Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of each of amlodipine ($C_{20}H_{25}N_2O_5Cl$) and benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$).

IDENTIFICATION

- A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY**• PROCEDURE**

Buffer 1: 0.7% (v/v) of triethylamine in water. Adjust with phosphoric acid to a pH of 3.0, and add 1.2 g of tetrabutyl ammonium hydrogen sulfate per 1 L of *Buffer*. Pass through a suitable filter of 0.45- μ m pore size.

Buffer 2: 7.0 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 3.0. Pass through a suitable filter of 0.45- μ m pore size.

Diluent: Acetonitrile, methanol, and *Buffer 2* (20:30:50)

Mobile phase: Acetonitrile, methanol, and *Buffer 1* (10:30:70)

Standard solution: Prepare the corresponding solutions in *Diluent* as directed in *Table 1*.

Table 1

Strength of Capsule (Amlodipine (mg)/ Benazepril Hydrochloride (mg))	Concentration of Amlodipine Besylate/Benazepril Hydrochloride (mg/mL)
2.5/10	0.18/0.5
5/20	0.18/0.5
5/10	0.18/0.25
10/20	0.36/0.5
5/40 and 10/40	0.04/0.16

Pass through a suitable membrane filter of 0.45- μ m pore size.

Sample solution: Transfer the contents of five Capsules into a volumetric flask as given in *Table 2*. Add *Diluent* (about 70% of the volume of the flask) and keep on a rotary shaker for about 45 min, sonicate for 30 min with occasional shaking, and dilute with *Diluent* to volume. Centrifuge a portion of the above solution at 3000 rpm for 10 min, and pass through a filter of 0.45- μ m pore size.

Table 2

Strength of Capsule (Amlodipine (mg)/ Benazepril Hydrochloride (mg))	Concentration of Amlodipine/Benazepril Hydrochloride (mg/mL)
2.5/10	0.125/0.5
5/20	0.125/0.5
5/10	0.125/0.25
10/20	0.25/0.5
5/40	0.02/0.16
10/40	0.04/0.16

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing L1

Flow rate: 1.2 mL/min

Injection volume: 10 μ L

Run time: Two times the retention time of amlodipine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both amlodipine and benazepril peaks

Relative standard deviation: NMT 2.0% for both amlodipine and benazepril peaks

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = response of the amlodipine peak from the *Sample solution*

r_S = response of the amlodipine peak from the *Standard solution*

C_S = concentration of amlodipine in the *Standard solution* (mg/mL)

C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of amlodipine, 408.88

M_{r2} = molecular weight of amlodipine besylate, 567.05

Calculate the percentage of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$), in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = response of the benazepril peak from the *Sample solution*

r_S = response of the benazepril peak from the *Standard solution*

C_S = concentration of benazepril hydrochloride in the *Standard solution* (mg/mL)

C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of amlodipine free base and 90.0%–110.0% of the labeled amount of benazepril hydrochloride

PERFORMANCE TESTS**• DISSOLUTION <711>**

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 30 min

Buffer: 2.72 g/L of potassium dihydrogen phosphate in water. Add 0.2% (v/v) of triethylamine per L. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile, methanol, and *Buffer* (15:35:50)

Amlodipine besylate standard stock solution:

0.385 mg/mL of USP Amlodipine Besylate RS in *Medium*

Benazepril hydrochloride standard stock solution:

0.225 mg/mL of USP Benazepril Hydrochloride RS in *Medium*

Standard solution: Dilute aliquots of the *Amlodipine besylate standard stock solution* and *Benazepril hydrochloride standard stock solution* with *Medium* as per *Table 3*.

Table 3

Strength of the Capsule (Amlodipine/Benazepril Hydrochloride) (mg/mg)	Volume of Amlodipine Besylate Standard Stock Solution/Volume of Benazepril Hydrochloride Standard Stock Solution (mL)	Volume of the Flask (mL)
2.5/10	1/5	50
5/10	2/5	50
5/20	2/10	50
10/20	2/5	25

For Tablet strengths 5/40 (Amlodipine/Benazepril Hydrochloride, mg/mg): 0.01 mg/mL of USP Amlodipine RS and 0.08 mg/mL of USP Benazepril Hydrochloride RS in *Medium*.

For Tablet strengths 10/40 (Amlodipine/Benazepril Hydrochloride, mg/mg): 0.02 mg/mL of USP Amlodipine RS and 0.08 mg/mL of USP Benazepril Hydrochloride RS in *Medium*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm \times 10-cm; 3- μ m packing L1

Flow rate: 1 mL/min

Injection volume: 50 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both amlodipine and benazepril peaks

Relative standard deviation: NMT 2.0% for both amlodipine and benazepril peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}N_2O_5Cl$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times 100$$

r_U = peak response for amlodipine from the *Sample solution*

r_S = peak response for amlodipine from the *Standard solution*

C_S = concentration of USP Amlodipine Besylate RS in the *Standard solution*

L = label claim for amlodipine (mg/Capsule)

M_{r1} = molecular weight of amlodipine, 408.88

M_{r2} = molecular weight of amlodipine besylate, 567.05

V = volume of *Medium*, 500 mL

Calculate the percentage of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response for benazepril from the *Sample solution*

r_S = peak response for benazepril from the *Standard solution*

C_S = concentration of benazepril hydrochloride in the *Standard solution*

L = label claim for benazepril hydrochloride (mg/Capsule)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amounts of amlodipine ($C_{20}H_{25}N_2O_5Cl$) and benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) are dissolved.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

IMPURITIES

• PROCEDURE

Buffer 1, Buffer 2, and Diluent: Proceed as directed in the *Assay*.

Solution A: Acetonitrile and *Buffer 1* (20:80)

Solution B: Methanol and *Buffer 1* (80:20)

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	85	15
100	30	70
101	85	15
110	85	15

Standard stock solution: 0.36 mg/mL of amlodipine and amlodipine related compound A and 1 mg/mL each of benazepril hydrochloride and benazepril related compound C solution in *Diluent*

Standard solution: 1 μ g/mL of amlodipine and amlodipine related compound A and 3 μ g/mL each of benazepril hydrochloride and benazepril related compound C solution in *Diluent*

Sample solution: 0.25 mg/mL of amlodipine from powdered Capsules (NLT 20). [NOTE—The benazepril hydrochloride concentration may vary depending on the ratio of amlodipine to benazepril hydrochloride in the Capsule.] Initially add *Diluent*, about 70% of the volume of the flask, sonicate for 30 min with intermittent shaking, and dilute with *Diluent* to volume. Pass through a membrane filter of 0.45- μ m pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 40 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both amlodipine and benazepril peaks

Resolution: NLT 2.0 between the amlodipine and benazepril peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amlodipine related compound A in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = response of amlodipine related compound A from the *Sample solution*

r_S = response of amlodipine related compound A from the *Standard solution*

C_S = concentration of amlodipine related compound A in the *Standard solution* (mg/mL)

C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of amlodipine related compound A, 408.88

M_{r2} = molecular weight of amlodipine related compound A fumarate, 522.93

Calculate the percentage of benazepril related compound C in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- r_U = response of benazepril related compound C from the *Sample solution*
 r_S = response of benazepril related compound C from the *Standard solution*
 C_S = concentration of benazepril related compound C in the *Standard solution* (mg/mL)
 C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any other impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_T) \times 100$$

- r_U = response of each other impurity from the *Sample solution*
 r_T = sum of responses of all peaks from the *Sample solution*

Acceptance criteria: See Table 5.

Table 5

Impurity Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benazepril related compound C ^a	0.23	3.0
Amlodipine related compound A ^b	0.44	1.0
Amlodipine	1.00	—
Benazepril	1.20	—
Any other individual unspecified impurity	—	0.2
Total impurities ^c	—	5.0

[NOTE—Disregard the peaks at relative retention times of 0.09 and 0.10.]

^a {3-[1-Carboxy-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid.

^b 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].

^c Total impurities include the sum of all impurities. The process-related impurities are not included.

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- USP REFERENCE STANDARDS (11)**
 - USP Amlodipine Besylate RS
 - USP Amlodipine Related Compound A RS
 - 3-Ethyl, 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate] fumarate.
 $C_{20}H_{23}ClN_2O_5 \cdot C_4H_4O_4$ 522.93
 - USP Benazepril Hydrochloride RS
 - USP Benazepril Related Compound C RS
 - 3-(1-Carboxy-3-phenyl-1(*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid.
 $C_{22}H_{24}N_2O_5$ 396.44 ■^{1S} (USP36)

Amoxapine Tablets

DEFINITION

Amoxapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of amoxapine ($C_{17}H_{16}ClN_3O$).

IDENTIFICATION

- A. INFRARED ABSORPTION (197K)**
Sample: Triturate a quantity of finely ground Tablets, equivalent to 50 mg of amoxapine, with 10 mL of chlo-

roform, and filter. Evaporate the filtrate on a steam bath to dryness (about 30 min).

Add the following:

- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay. ■^{1S} (USP36)

ASSAY

PROCEDURE

Solution A: 1.38 g/L of monobasic sodium phosphate in water

Solution B: 113 g/L of tetramethylammonium chloride in water

Mobile phase: Transfer 20.0 mL of *Solution B*, 4.0 mL of dilute phosphoric acid (1 in 5), and 720 mL of acetonitrile to a 2000-mL volumetric flask. Dilute with *Solution A* to volume.

Standard stock solution: 1 mg/mL of USP Amoxapine RS in acetonitrile. Shake by mechanical means to dissolve, and then dilute with acetonitrile to volume.

Standard solution: 0.1 mg/mL from the *Standard stock solution* diluted with *Mobile phase*

Sample stock solution: Nominally 1 mg/mL of amoxapine from NLT 20 finely powdered Tablets prepared as follows. Transfer a suitable quantity of the powder to a volumetric flask. Add 80% of the flask volume of *Mobile phase*, and shake vigorously by mechanical means for 20 min. Dilute with *Mobile phase* to volume, and filter.

Sample solution: 0.1 mg/mL from the *Sample stock solution* diluted with *Mobile phase*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1200 theoretical plates

Tailing factor: NMT 1.8

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amoxapine ($C_{17}H_{16}ClN_3O$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of amoxapine from the *Sample solution*

r_S = peak response of amoxapine from the *Standard solution*

C_S = concentration of USP Amoxapine RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of amoxapine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

DISSOLUTION (711)

Medium: Simulated gastric fluid (without enzyme); 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Sample solution: Sample per *Dissolution* <711>.

Standard solution: USP Amoxapine RS having a concentration similar to the expected *Sample solution* in *Medium*

Instrumental conditions

Analytical wavelength: 294 nm

Analysis

■ **Samples:** *Sample solution* and *Standard solution* ■ **1S** (USP36)

Determine the percentage of the labeled amount of amoxapine ($C_{17}H_{16}ClN_3O$) dissolved from UV absorbances of filtered portions of the *Sample solution*, suitably diluted with *Medium*, if necessary.

■ Calculate the percentage of the labeled amount of amoxapine ($C_{17}H_{16}ClN_3O$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*
 A_S = absorbance of the *Standard solution*
 C_S = concentration of the *Standard solution* (mg/mL)
 V = volume of the *Medium*, 900 mL
 L = label claim (mg/Tablet)

■ **1S** (USP36)

Tolerances: NLT 80% (Q) of the labeled amount of amoxapine ($C_{17}H_{16}ClN_3O$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **USP REFERENCE STANDARDS** <11>
USP Amoxapine RS

Add the following:

Amoxicillin and Clavulanic Acid Extended-Release Tablets

DEFINITION

Amoxicillin and Clavulanic Acid Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanic acid ($C_8H_9NO_5$).

IDENTIFICATION

- **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Buffer: 6.9 g/L of monobasic sodium phosphate adjusted with phosphoric acid to a pH of 4.2

Mobile phase: Methanol and *Buffer* (5:95)

Standard solution: 1 mg/mL of USP Amoxicillin RS and 62.5 µg/mL of USP Clavulanate Lithium RS in water. Store the solution at 4°, and inject within 10 h.

Sample solution: Equivalent to 1 mg/mL of amoxicillin and 62.5 µg/mL of clavulanic acid from finely powdered Tablets (NLT 6) in water. Stir for about 60 min. Store the solution at 4°, and inject within 12 h.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 229 nm

Column: 8-mm × 10-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

Autosampler temperature: 4°

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between the amoxicillin and clavulanic acid peaks

Tailing factor: NMT 1.8 for the amoxicillin and clavulanic acid peaks

Relative standard deviation: NMT 1.0% for the amoxicillin and clavulanic acid peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = response of amoxicillin from the *Sample solution*
 r_S = response of amoxicillin from the *Standard solution*
 C_S = concentration of USP Amoxicillin RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of amoxicillin in the *Sample solution* (mg/mL)
 P = potency of amoxicillin in USP Amoxicillin RS (µg/mg)
 F = conversion factor, 0.001 mg/µg

Calculate the percentage of the labeled amount of clavulanic acid ($C_8H_9NO_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = response of clavulanic acid from the *Sample solution*
 r_S = response of clavulanic acid from the *Standard solution*
 C_S = concentration of USP Clavulanate Lithium RS in the *Standard solution* (µg/mL)
 C_U = nominal concentration of clavulanic acid in the *Sample solution* (µg/mL)
 P = potency of clavulanic acid in USP Clavulanate Lithium RS (mg/mg)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

DISSOLUTION <711>

Medium: Water; 900 mL

Apparatus 2: 75 rpm

Times

Amoxicillin: 1, 3, and 5 h

Clavulanic acid: 1 h

Mobile phase, Chromatographic system, and System suitability: Proceed as directed in the *Assay*.

Standard solution: USP Amoxicillin RS and USP Clavulanate Lithium RS in *Medium* at known concentrations similar to those expected in the *Sample solution*

Sample solution: Pass a portion of the solution under test through a suitable filter, and dilute with *Medium*, if necessary.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the amounts of amoxicillin ($C_{16}H_{19}N_3O_5S$) and clavulanic acid ($C_8H_9NO_5$) dissolved.

Tolerances

Amoxicillin: The percentage of the labeled amount of amoxicillin ($C_{16}H_{19}N_3O_5S$) dissolved at the times specified conforms to *Table 1*.

Table 1

Time (h)	Amount Dissolved (%)
1	50–65
3	65–85
5	NLT 85

Clavulanic acid: NLT 80% (Q) of the labeled amount of clavulanic acid ($C_8H_9NO_5$) is dissolved in 1 h.

- UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES**• ORGANIC IMPURITIES**

Buffer: 13.8 g/L of monobasic sodium phosphate in water adjusted with phosphoric acid to a pH of 4.2

Solution A: Methanol and *Buffer* (1:199)

Solution B: Methanol and *Buffer* (10:90)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
8	70	30
13	70	30
13.01	40	60
18	40	60
18.01	100	0
25	100	0
30	100	0

[NOTE—These gradient elution times are established on an HPLC system with a dwell volume of approximately 5 mL. The gradient elution times in *Table 2* can be adjusted as necessary to achieve the separation described.]

System suitability solution: 0.4 mg/mL of USP Amoxicillin RS and 30 µg/mL of USP Amoxicillin Related Compound D RS in water. Store the solution at 4°.

Standard solution: 0.4 mg/mL of USP Amoxicillin RS in water. Store the solution at 4°, and inject within 24 h.

Sample solution: 1 mg/mL of amoxicillin and 62.5 µg/mL of clavulanic acid from finely powdered Tablets (NLT 2) in water. Stir for about 60 min. Store the solution at 4°, and use within 24 h.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 5-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Autosampler temperature: 4°

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.25 between the amoxicillin and amoxicillin related compound D peaks at a relative retention time of 0.83, *System suitability solution*

Tailing factor: NMT 1.8 for the amoxicillin peak, *Standard solution*

Relative standard deviation: NMT 1.0% for the amoxicillin peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F_1 \times (1/F_2) \times 100$$

r_U = response of each impurity from the *Sample solution*

r_S = response of amoxicillin from the *Standard solution*

C_S = concentration of USP Amoxicillin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of amoxicillin in the *Sample solution* (mg/mL)

P = potency of amoxicillin in USP Amoxicillin RS (µg/mg)

F_1 = conversion factor, 0.001 mg/µg

F_2 = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting limit is 0.003%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amoxicillin related compound I (D-hydroxyphenyl-glycine) ^{a,b}	0.15	—	—
Amoxicillin related compound A (6-aminopenicillanic acid) ^{a,c}	0.30	—	—
Clavulanic acid	0.39	—	—
Amoxicillin related compound D (amoxicillin open ring) ^{a,d,e}	0.63	0.74	—
Amoxicillin related compound B (L-amoxicillin) ^{a,f}	0.78	—	—
Amoxicillin related compound D (amoxicillin open ring) ^{a,g}	0.83	0.74	2.5
Amoxicillin	1.0	—	—

^a These are synthetic process impurities, which are controlled in the drug substance. They are listed here for reference only and are not to be reported.

^b (R)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

^c (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^d The chromatographic system resolves two isomers of amoxicillin open ring.

^e (4S)-2-[[[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^f (2S,5R,6R)-6-[(S)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^g (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^h The chromatographic system resolves two amoxicillin penilloic derivatives.

ⁱ (4S)-2-[[[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](methyl)-5,5-dimethylthiazolidine-4-carboxylic acid.

^j (4S)-2-[[5-(4-Hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^k (4S)-2-[[[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]methoxy-carbonylmethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^l (2S,5R,6R)-6-[(2R)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Table 3 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amoxicillin related compound G (D-hydroxyphenylglycylamoxicillin) ^{a,g}	2.57	—	—
Amoxicillin related compound E (amoxicillin penilloic derivatives) ^{a,h,i}	2.63	—	—
	3.00	—	—
Amoxicillin related compound C (amoxicillin rearrangement product) ⁱ	3.22	1.1	2.5
Amoxicillin open ring methyl ester ^{a,k}	3.38	—	—
Amoxicillin related compound J (amoxicillin open ring dimer) ⁱ	4.07	1.0	4.5
Any individual unspecified impurity	—	—	0.5

^a These are synthetic process impurities, which are controlled in the drug substance. They are listed here for reference only and are not to be reported.

^b (R)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

^c (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^d The chromatographic system resolves two isomers of amoxicillin open ring.

^e (4S)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^f (2S,5R,6R)-6-[(S)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^g (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^h The chromatographic system resolves two amoxicillin penilloic derivatives.

ⁱ (4S)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^j (4S)-2-[5-(4-Hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^k (4S)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]methoxycarbonylmethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^l (2S,5R,6R)-6-[(2R)-2-[2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

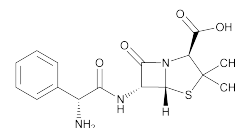
SPECIFIC TESTS

- MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count does not exceed 10^3 cfu/g, and the total combined molds and yeasts count does not exceed 10^2 cfu/g.

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- USP REFERENCE STANDARDS** (11)
 - USP Amoxicillin RS
 - USP Amoxicillin Related Compound D RS
 - (4S)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.
 - C₁₆H₂₁N₃O₆S 383.42
 - USP Clavulanate Lithium RS^{11S} (USP36)

Ampicillin



C₁₆H₁₉N₃O₄S (anhydrous) 349.41
 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, [6-(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, [2S-[2 α ,5 α ,6 β (S*)]]-;
 (2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid [69-53-4].
 Trihydrate 403.46
 [7177-48-2].

DEFINITION

Ampicillin is anhydrous or contains three molecules of water of hydration. It contains NLT 900 μ g/mg and NMT 1050 μ g/mg of ampicillin (C₁₆H₁₉N₃O₄S), calculated on the anhydrous basis.

IDENTIFICATION

- INFRARED ABSORPTION** (197K): Except that where the specimen under test is the trihydrate, both it and the USP Ampicillin Trihydrate RS are undried.

ASSAY

Change to read:

PROCEDURE

Solution A: 6.54 g/L of monobasic potassium phosphate and 0.34 g/L of dibasic potassium phosphate, adjusted with 1 N sodium hydroxide or 1 N phosphoric acid to a pH of 5.5 before final dilution

Solution B: Acetonitrile and *Solution A* (2:23)

Solution C: Acetonitrile and *Solution A* (3:7)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
6	100	0
15	0	100
16	0	100
18	100	0
20	100	0

Solution D: 46.3 g/L of monobasic potassium phosphate and 27.8 g/L of dibasic potassium phosphate, adjusted with 1 N sodium hydroxide or 1 N phosphoric acid to a pH of 6.5 before final dilution

System suitability solution: 0.5 mg/mL of USP Ampicillin RS and 0.1 mg/mL of USP Amoxicillin RS in acetonitrile, water, and *Solution D* (4:91:5) prepared as follows. Dissolve first in a mixture of acetonitrile, water, and *Solution D* (4:30:5), sonicating if necessary, and dilute with water to volume.

Standard solution: 0.5 mg/mL of USP Ampicillin RS in acetonitrile, water, and *Solution D* (4:91:5) prepared as follows. Dissolve first in a mixture of acetonitrile, water, and *Solution D* (4:30:5), sonicating if necessary, and dilute with water to volume. Analyze immediately after preparation.

Sample solution: 0.5 mg/mL of Ampicillin in acetonitrile, water, and *Solution D* (4:91:5) prepared as follows. Dissolve first in a mixture of acetonitrile, water, and *Solution D* (4:30:5), sonicating if necessary, and dilute with water to volume.

lution D (4:30:5), sonicating if necessary, and dilute with water to volume. Analyze immediately after preparation.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 15-cm; 5-μm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 μL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 10 between ampicillin and amoxicillin, *System suitability solution*

Tailing factor: NMT 1.4 for ampicillin, $\mathbf{1S}$ (USP36) *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in μg, of ampicillin ($C_{16}H_{19}N_3O_4S$) in each mg of Ampicillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Ampicillin RS in the *Standard solution* (mg/mL)

C_U = concentration of Ampicillin in the *Sample solution* (mg/mL)

P = potency of USP Ampicillin RS (μg/mg)

Acceptance criteria: 900–1050 μg/mg $\mathbf{1S}$ (USP36) on the anhydrous basis

IMPURITIES

Change to read:

• ORGANIC IMPURITIES, PROCEDURE 1

Organic Impurities, Procedure 1 is recommended when the impurity profile includes ampicillin thiazepine. $\mathbf{1S}$ (USP36)

Solution A, Solution B, Solution C, Mobile phase, Solution D, System suitability solution, Sample solution, and **Chromatographic system:** Prepare as directed in the Assay.

Standard stock solution: Prepare as directed for the *Standard solution* in the Assay.

Standard solution: 0.005 mg/mL of ampicillin in *Solution D* and water (1:19) from *Standard stock solution*. Transfer an aliquot of the *Standard stock solution* to a suitable volumetric flask, add *Solution D*, using about 5% of the final volume, and dilute with water to volume. Analyze immediately after preparation.

Sensitivity solution: 0.5 μg/mL of ampicillin in *Solution D* and water (1:19) from the *Standard solution*. Transfer an aliquot of the *Standard solution* to a suitable volumetric flask, add *Solution D*, using about 5% of the final volume, and dilute with water to volume.

System suitability

Samples: *Sensitivity solution*, *System suitability solution*, and *Standard solution*

Suitability requirements

Signal-to-noise ratio: NLT 3, *Sensitivity solution*

Resolution: NLT 10 between ampicillin and amoxicillin, *System suitability solution*

Tailing factor: NMT 1.4 for ampicillin, $\mathbf{1S}$ (USP36) *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Ampicillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of ampicillin from the *Standard solution*

C_S = concentration of USP Ampicillin RS in the *Standard solution* (mg/mL)

C_U = concentration of Ampicillin in the *Sample solution* (mg/mL)

P = potency of USP Ampicillin RS (μg/mg)

F = conversion factor, 0.001 mg/μg

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
D-Phenylglycine ^a	0.27	0.5
Amoxicillin related compound A (6-aminopenicillanic acid) $\mathbf{1S}$ (USP36)^b	0.31	0.5
Ampicilloic acid ^c	0.45	1.0
Ampicillin thiazepine analog ^d	0.65	0.3
Ampicillin	1.0	—
Ampicillin rearrangement product (isomer 1) ^e	1.8	0.4
Ampicillin rearrangement product (isomer 2) ^e	2.0	0.3
Ampicillin oligomer 2 ^f	2.2	0.6
D-Phenylglycylampicillin ^g	2.5	0.8
Ampicillin oligomer 1 (dimer) ^h	2.6	1.0
Ampicillin oligomer 1 (trimer) ⁱ	2.9	0.4
Any individual unspecified impurity	—	0.25
Total impurities	—	3.0

^a (R)-2-Amino-2-phenylacetic acid.

^b (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^c (4S)-2-[(R)-2-Amino-2-phenylacetamido](carboxy)methyl-5,5-dimethylthiazolidine-4-carboxylic acid.

^d (S)-6-[(R)-2-Amino-2-phenylacetamido]-2,2-dimethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine-3-carboxylic acid.

^e (4S)-2-(3,6-Dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid.

^f (4S)-2-[1-[(R)-2-Amino-2-phenylacetamido]-2-[(1R)-2-(carboxy[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^g (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^h (2S,5R,6R)-6-[(2R)-2-[2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

ⁱ (4S,4'S)-2,2'-[(1R,7R,13R)-1-Amino-14-[(2S,5R,6R)-2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-ylamino]-2,5,8,11,14-penta-oxo-1,7,13-triphenyl-3,6,9,12-tetraazatetradecane-4,10-diyl]bis(5,5-dimethylthiazolidine-4-carboxylic acid).

Change to read:**• ORGANIC IMPURITIES, PROCEDURE 2, DIMETHYLANILINE (223):**
Meets the requirements

■ *Organic Impurities, Procedure 2* is recommended when dimethylaniline is used during the production of Ampicillin. ■ ¹⁵ (USP36)

Add the following:**■ ORGANIC IMPURITIES, PROCEDURE 3**

Organic Impurities, Procedure 3 is recommended when the impurity profile includes phenylpyrazinol, pivaloyl phenylglycine, pivaloyl aminopenicillanic acid, diphenyldiketopiperazine, and open ring dimer.

Solution A: 4 g/L of monobasic sodium phosphate dihydrate adjusted with 1 N sodium hydroxide to a pH of 5.0

Solution B: Acetonitrile

Mobile phase: See Table 3.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	98	2
20	90	10
40	85	15
50	80	20
55	75	25
60	75	25
62	98	2
70	98	2

Diluent: Acetonitrile and *Solution A* (2:98)

System suitability solution: 1.5 mg/mL of USP Ampicillin System Suitability Mixture RS in *Diluent*

Standard solution: 15 µg/mL of USP Ampicillin RS in *Diluent*

Sample solution: 1.5 mg/mL of Ampicillin in *Diluent*. Store the sample in the refrigerator, and discard after 60 min.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Autosampler temperature: 4°

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between the pivaloyl phenylglycine and diphenyldiketopiperazine peaks, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Ampicillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of ampicillin from the *Standard solution*

C_S = concentration of USP Ampicillin RS in the *Standard solution* (mg/mL)

C_U = concentration of Ampicillin in the *Sample solution* (mg/mL)

P = potency of ampicillin in USP Ampicillin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: See Table 4 and Table 5. The limits in Table 5 are to be used only where Ampicillin is intended for use in preparing veterinary products.

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
D-Phenylglycine ^a	0.15	1.0
Amoxicillin related compound A (6-aminopenicillanic acid) ^b	0.21	1.0
Ampicilloic acid ^{c,d}	0.40	1.0
	0.58	
L-Ampicillin ^e	0.65	1.0
Ampicillin	1.0	—
Ampicilloic acid ^{f,g}	1.16	1.0
	1.40	
Ampicillin rearrangement product ^{h,i}	1.25	1.0
	1.48	
Phenylpyrazinol ^j	1.75	1.0
Pivaloyl phenylglycine ^k	1.87	1.0
Diphenyldiketopiperazine ^l	1.94	1.0
Ampicillin oligomer 2 ^m	2.08	1.0
D-Phenylglycylampicillin ⁿ	2.25	1.0

^a (R)-2-Amino-2-phenylacetic acid.

^b (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^c (4S)-2-[[[(R)-2-Amino-2-phenylacetamido](carboxy)methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^d The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.

^e (2S,5R,6R)-6-[(S)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^f (4S)-2-[[[(R)-2-Amino-2-phenylacetamido]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^g The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.

^h (4S)-2-(3,6-Dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid.

ⁱ The system resolves the two isomers of ampicillin rearrangement product. The sum of the two isomers is reported.

^j 3-Phenylpyrazinol.

^k (R)-2-Phenyl-2-pivalamidoacetic acid.

^l 3,6-Diphenylpiperazine-2,5-dione.

^m (4S)-2-[1-[(R)-2-Amino-2-phenylacetamido]-2-[(1R)-2-(carboxy[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

ⁿ (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^o (2S,5R,6R)-3,3-Dimethyl-7-oxo-6-pivalamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^p (4S)-2-[1-[(R)-2-amino-2-phenylacetamido]-2-[(1R)-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino]-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.

^q The system may resolve the three isomers of open ring dimer. The sum of the three isomers is reported.

^r (2S,5R,6R)-6-[(2R)-2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

^s (R)-2-[(2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-2-phenylacetic acid.

^t (4S,4'S)-2,2'-[(1R,7R,13R)-1-Amino-14-[(2S,5R,6R)-2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-ylamino]-2,5,8,11,14-penta-oxo-1,7,13-triphenyl-3,6,9,12-tetraazatetradecane-4,10-diyl]bis(5,5-dimethylthiazolidine-4-carboxylic acid).

Table 4 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Pivaloyl aminopenicillanic acid ^a	2.54	1.0
Open ring dimer ^{b,q}	2.87	1.0
	2.97	
	3.03	
Ampicillin oligomer 1 (dimer) ^r	3.15	1.0
Ampicillinyl-D-phenylglycine ^s	3.86	1.0
Ampicillin oligomer 1 (trimer) ^t	4.19	1.0
Any individual unspecified impurity	—	0.10
Total impurities	—	5.0

^a (R)-2-Amino-2-phenylacetic acid.^b (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^c (4S)-2-[(R)-2-Amino-2-phenylacetamido](carboxymethyl)-5,5-dimethylthiazolidine-4-carboxylic acid.^d The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.^e (2S,5R,6R)-6-[(S)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^f (4S)-2-[(R)-2-Amino-2-phenylacetamido]methyl-5,5-dimethylthiazolidine-4-carboxylic acid.^g The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.^h (4S)-2-(3,6-Dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid.ⁱ The system resolves the two isomers of ampicillin rearrangement product. The sum of the two isomers is reported.^j 3-Phenylpyrazin-2-ol.^k (R)-2-Phenyl-2-pivalamidoacetic acid.^l 3,6-Diphenylpiperazine-2,5-dione.^m (4S)-2-[1-[(R)-2-Amino-2-phenylacetamido]-2-[(1R)-2-(carboxy[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.ⁿ (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^o (2S,5R,6R)-3,3-Dimethyl-7-oxo-6-pivalamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^p (4S)-2-[1-[(R)-2-amino-2-phenylacetamido]-2-[(1R)-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^q The system may resolve the three isomers of open ring dimer. The sum of the three isomers is reported.^r (2S,5R,6R)-6-[(2R)-2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^s (R)-2-[(2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-2-phenylacetic acid.^t (4S,4'S)-2,2'-[(1R,7R,13R)-1-Amino-14-[(2S,5R,6R)-2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-ylamino]-2,5,8,11,14-penta-oxo-1,7,13-triphenyl-3,6,9,12-tetraazatetradecane-4,10-diyl]bis[(S,5-dimethylthiazolidine-4-carboxylic acid).

Where it is intended for use in preparing veterinary products:

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
D-Phenylglycine ^a	0.15	2.0
Amoxicillin related compound A (6-aminopenicillanic acid) ^b	0.21	2.0
N-Formyl ampicilloic acid ^c	0.26	1.0
Ampicilloic acid ^{d,e}	0.40	2.0
	0.58	
L-Ampicillin ^f	0.65	2.0
Ampicillin	1.0	—
Ampilloic acid ^{g,h}	1.16	2.0
	1.40	
Ampicillin rearrangement product ^{i,j}	1.25	2.0
	1.48	
Phenylpyrazinol ^k	1.75	2.0
Pivaloyl phenylglycine ^l	1.87	2.0
Diphenyldiketopiperazine ^m	1.94	2.0
Ampicillin oligomer 2 ⁿ	2.08	2.0
D-Phenylglycylampicillin ^o	2.25	2.0
Pivaloyl aminopenicillanic acid ^p	2.54	2.0
Open ring dimer ^{q,r}	2.87	0.50
	2.97	0.50
	3.03	0.50
Ampicillin oligomer 1 (dimer) ^s	3.15	4.5

^a (R)-2-Amino-2-phenylacetic acid.^b (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^c (4S)-2-[(R)-2-Amino-2-phenylacetamido](carboxymethyl)-3-formyl-5,5-dimethylthiazolidine-4-carboxylic acid.^d (4S)-2-[(R)-2-Amino-2-phenylacetamido](carboxymethyl)-5,5-dimethylthiazolidine-4-carboxylic acid.^e The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.^f (2S,5R,6R)-6-[(S)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^g (4S)-2-[(R)-2-Amino-2-phenylacetamido]methyl-5,5-dimethylthiazolidine-4-carboxylic acid.^h The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.ⁱ (4S)-2-(3,6-Dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid.^j The system resolves the two isomers of ampicillin rearrangement product. The sum of the two isomers is reported.^k 3-Phenylpyrazin-2-ol.^l (R)-2-Phenyl-2-pivalamidoacetic acid.^m 3,6-Diphenylpiperazine-2,5-dione.ⁿ (4S)-2-[1-[(R)-2-Amino-2-phenylacetamido]-2-[(1R)-2-(carboxy[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^o (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^p (2S,5R,6R)-3,3-Dimethyl-7-oxo-6-pivalamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^q (4S)-2-[1-[(R)-2-amino-2-phenylacetamido]-2-[(1R)-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^r The system may resolve the three isomers of open ring dimer.^s (2S,5R,6R)-6-[(2R)-2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^t (R)-2-[(2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-2-phenylacetic acid.^u (4S,4'S)-2,2'-[(1R,7R,13R)-1-Amino-14-[(2S,5R,6R)-2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-ylamino]-2,5,8,11,14-penta-oxo-1,7,13-triphenyl-3,6,9,12-tetraazatetradecane-4,10-diyl]bis[(S,5-dimethylthiazolidine-4-carboxylic acid).

Table 5 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Ampicillinyl-D-phenylglycine ^a	3.86	2.0
Ampicillin oligomer 1 (trimer) ^u	4.19	2.0
Any individual unspecified impurity	—	0.5
Total impurities	—	5.0

^a (R)-2-Amino-2-phenylacetic acid.^b (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^c (4S)-2-[(R)-2-Amino-2-phenylacetamido](carboxy)methyl-3-formyl-5,5-dimethylthiazolidine-4-carboxylic acid.^d (4S)-2-[(R)-2-Amino-2-phenylacetamido](carboxy)methyl-5,5-dimethylthiazolidine-4-carboxylic acid.^e The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.^f (2S,5R,6R)-6-[(S)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^g (4S)-2-[(R)-2-Amino-2-phenylacetamido]methyl-5,5-dimethylthiazolidine-4-carboxylic acid.^h The system resolves the two isomers of ampicilloic acid. The sum of the two isomers is reported.ⁱ (4S)-2-(3,6-Dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid.^j The system resolves the two isomers of ampicillin rearrangement product. The sum of the two isomers is reported.^k 3-Phenylpiperazin-2-ol.^l (R)-2-Phenyl-2-pivalamidoacetic acid.^m 3,6-Diphenylpiperazine-2,5-dione.ⁿ (4S)-2-[1-[(R)-2-Amino-2-phenylacetamido]-2-[(1R)-2-(carboxy[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^o (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^p (2S,5R,6R)-3,3-Dimethyl-7-oxo-6-pivalamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^q (4S)-2-[1-[(R)-2-amino-2-phenylacetamido]-2-[(1R)-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]methylamino)-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^r The system may resolve the three isomers of open ring dimer.^s (2S,5R,6R)-6-[(2R)-2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^t (R)-2-[(2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-ylamino]-2-oxo-1-phenylethylamino]-2-oxoethyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^u (4S,4'S)-2,2'-[(1R,7R,13R)-1-Amino-14-[(2S,5R,6R)-2-carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptan-6-ylamino]-2,5,8,11,14-penta-oxo-1,7,13-triphenyl-3,6,9,12-tetraazatetradecane-4,10-diyl]bis(5,5-dimethylthiazolidine-4-carboxylic acid).

■ IS (USP36)

Add the following:**■ ORGANIC IMPURITIES, PROCEDURE 4**

Organic Impurities, Procedure 4 is recommended when the impurity profile includes ampicilloyl aminopenicillanic acid and penicillanyl ampicillinamide.

Solution A: 3.4 g/L of dibasic sodium phosphate dodecahydrate and 1.4 g/L of monobasic potassium phosphate adjusted with phosphoric acid to a pH of 5.5

Solution B: Acetonitrile

Mobile phase: See Table 6.

Table 6

Time (min)	Solution A (%)	Solution B (%)
0	99	1
1.5	95	5
6.5	90	10
7.5	89	11

Table 6 (Continued)

Time (min)	Solution A (%)	Solution B (%)
13.5	84	16
16.5	75	25
18	60	40
25	99	1

Standard solution: 30 µg/mL of USP Amoxicillin Related Compound A RS, 30 µg/mL of D-phenylglycine, and 25 µg/mL of USP Ampicillin RS in *Solution A*

Sample solution: 2.5 mg/mL of Ampicillin in *Solution A*. Store the *Sample solution* in the refrigerator, and use within 9 h.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.0-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.3 mL/min

Injection volume: 5 µL

Autosampler temperature: 4°

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between D-phenylglycine and amoxicillin related compound A

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Ampicillin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of ampicillin from the *Standard solution*

C_S = concentration of USP Ampicillin RS in the *Standard solution* (mg/mL)

C_U = concentration of Ampicillin in the *Sample solution* (mg/mL)

P = potency of ampicillin in USP Ampicillin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: See Table 7. Disregard any peak with an area less than 0.03 times the area of the ampicillin peak in the *System suitability solution*.

Table 7

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
D-Phenylglycine ^a	0.21	0.5
Amoxicillin related compound A (6-aminopenicillanic acid) ^b	0.32	0.5
Ampicilloic acid ^c	0.46	1.0
	0.57	1.0
Ampicillin thiazepine analog ^{d,e}	0.72	—
L-Ampicillin ^f	0.84	0.5
Ampilloyl aminopenicillanic acid ^g	0.87	0.5
Ampicillin	1.00	—
	1.15	1.0
Ampilloic acid ^h	1.34	1.0
Ampicillin rearrangement product ⁱ	1.24	1.0
Pivaloyl phenylglycine ^j	1.47	—
Phenylpyrazinol ^{e,k}	1.84	—
Diphenyldiketopiperazine ^{e,l}	1.94	—
Pivaloyl aminopenicillanic acid ^{e,m}	1.95	—
D-Phenylglycylampicillin ⁿ	2.08	1.0
Ampicillin oligomer 1 (dimer) ^o	2.16	1.0
Penicillanyl ampicillinamide ^p	2.27	1.0
Ampicillinyl-D-phenylglycine ^q	2.64	1.0
Any individual unspecified impurity	—	1.0
Total impurities	—	5.0

^a (R)-2-Amino-2-phenylacetic acid.^b (2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^c (4S)-2-[[[(R)-2-Amino-2-phenylacetamido](carboxy)methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.^d (S)-6-[(R)-2-Amino-2-phenylacetamido]-2,2-dimethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine-3-carboxylic acid.^e These impurities are listed for information only. They are not to be reported. They are not to be included in total impurities.^f (2S,5R,6R)-6-[(S)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^g (2S,5R,6R)-6-{2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^h (4S)-2-[[[(R)-2-Amino-2-phenylacetamido]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid.ⁱ (4S)-2-(3,6-Dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid.^j (R)-2-Phenyl-2-pivalamidoacetic acid.^k 3-Phenylpyrazin-2-ol.^l 3,6-Diphenylpiperazine-2,5-dione.^m (2S,5R,6R)-3,3-Dimethyl-7-oxo-6-pivalamido-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.ⁿ (2S,5R,6R)-6-[(R)-2-[(R)-2-Amino-2-phenylacetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^o (2S,5R,6R)-6-[(2R)-2-[2-[(R)-2-Amino-2-phenylacetamido]-2-[(4S)-4-carboxy-5,5-dimethylthiazolidin-2-yl]acetamido]-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^p (2S,5R,6R)-6-[(2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.^q (R)-2-[(2S,5R,6R)-6-[(R)-2-Amino-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido]-2-phenylacetic acid.

■1S (USP36)

SPECIFIC TESTS**• STERILITY TESTS <71>**

Sample solution: Dissolve 6 g in 800 mL of *Fluid D* containing sufficient sterile penicillinase to inactivate the ampicillin, and swirl the vessel until dissolution is complete before filtering.

Acceptance criteria: Where the label states that Ampicillin is sterile, it meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*.

- **CRYSTALLINITY <695>:** Meets the requirements

- **PH <791>**

Sample solution: 10 mg/mL

Acceptance criteria: 3.5–6.0

- **WATER DETERMINATION, Method I <921>:** NMT 2.0% where it is labeled as Ampicillin (anhydrous); between 12.0% and 15.0% where it is labeled as Ampicillin (trihydrate)
- **BACTERIAL ENDOTOXINS TEST <85>:** Where the label states that Ampicillin is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.15 USP Endotoxin Unit/mg of ampicillin.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

- **LABELING:** Label to indicate whether it is anhydrous or is the trihydrate. Where the quantity of ampicillin is indicated in the labeling of any preparation containing Ampicillin, this shall be understood to be in terms of anhydrous ampicillin (C₁₆H₁₉N₃O₄S). Where it is intended for use in preparing injectable dosage forms, the label states that it is the trihydrate and that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

■ If a test for *Organic Impurities* other than *Procedures 1* and *2* is used, then the labeling states with which *Organic Impurities* test the article complies. Where it is intended for use in preparing veterinary products, the label so states. ■1S (USP36)

Change to read:**• USP REFERENCE STANDARDS <11>**

USP Amoxicillin RS

■ USP Amoxicillin Related Compound A RS

(2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

C₁₆H₁₄N₂O₂ 266.29 ■1S (USP36)

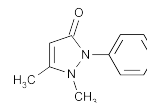
USP Ampicillin RS

■ USP Ampicillin System Suitability Mixture RS

This is a mixture which contains ampicillin, pivaloyl phenylglycine [(R)-2-phenyl-2-pivalamidoacetic acid; C₁₃H₁₇NO₃; 235.28], diphenyldiketopiperazine (3,6-diphenylpiperazine-2,5-dione; C₁₆H₁₄N₂O₂; 266.29), and other related compounds. ■1S (USP36)

USP Ampicillin Trihydrate RS

USP Endotoxin RS

Antipyrine

C₁₁H₁₂N₂O

188.23

1,2-Dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one;
2,3-Dimethyl-1-phenyl-3-pyrazolin-5-one [60-80-0].

DEFINITION

Antipyrine contains NLT 99.0% and NMT 100.5% of antipyrine (C₁₁H₁₂N₂O), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)
- **B. ULTRAVIOLET ABSORPTION** (197U)
Analytical wavelength: 266 nm
Sample solution: 20 µg/mL in methanol
Acceptance criteria: Absorptivities calculated on the dried basis do not differ by more than 3.0%.
- **C.**
Analysis: Add tannic acid TS to a solution of it.
Acceptance criteria: A white precipitate is formed.

ASSAY• **PROCEDURE**

Sample: 150 mg
Titrimetric system
(See *Titrimetry* (541).)
Mode: Residual titration
Titrant: 0.1 N sodium thiosulfate VS
Endpoint detection: Visual
Analysis: Dissolve the *Sample* in 25 mL of water in a 250-mL iodine flask. Add 2 g of sodium acetate, 1 mL of diluted acetic acid, and 20.0 mL of 0.1 N iodine VS to the *Sample* and allow to stand in a cool, dark place for 20 min. Add 25 mL of alcohol to dissolve the precipitate, and titrate the excess iodine with *Titrant*, using starch TS as the indicator. Each mL of 0.1 N iodine is equivalent to 9.412 mg of antipyrine (C₁₁H₁₂N₂O).
Acceptance criteria: 99.0%–100.5% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.15%
- **HEAVY METALS** (231)
Test preparation: Dissolve 1 g in 2 mL of 1 N acetic acid, and add water to make 25 mL.
Acceptance criteria: NMT 20 ppm

Change to read:• **ORGANIC IMPURITIES**

■ **Buffer:** Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water, add 2 mL of triethylamine, and adjust with 5 N sodium hydroxide solution to a pH of 7.0.
Mobile phase: Methanol and *Buffer* (43:100)
System suitability solution: 5 µg/mL each of USP Antipyrine RS and USP Antipyrine Related Compound A RS in *Mobile phase*
Standard solution: 0.5 µg/mL and 0.25 µg/mL of USP Antipyrine RS and USP Antipyrine Related Compound A RS, respectively, in *Mobile phase*
Sample solution: 500 µg/mL of Antipyrine in *Mobile phase*
Chromatographic system
(See *Chromatography* (621), *System Suitability*).
Mode: LC
Detector: UV 254 nm
Column: 6.0-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: Three times the retention time of antipyrine
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 3.0 between antipyrine related compound A and antipyrine
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of antipyrine related compound A in the portion of Antipyrine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of antipyrine related compound A from the *Sample solution*
 r_S = peak response of antipyrine related compound A from the *Standard solution*
 C_S = concentration of USP Antipyrine Related Compound A RS in the *Standard solution* (µg/mL)
 C_U = concentration of the *Sample solution* (µg/mL)
Calculate the percentage of any individual unspecified impurity in the portion of Antipyrine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of any individual unspecified impurity from the *Sample solution*
 r_S = peak response of antipyrine from the *Standard solution*
 C_S = concentration of USP Antipyrine RS in the *Standard solution* (µg/mL)
 C_U = concentration of the *Sample solution* (µg/mL) ■^{1S} (USP36)
Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Antipyrine related compound A ^a	0.8	0.05
Antipyrine	1.0	—
Individual unspecified impurity	—	0.05
Total impurities ^b	—	0.1

^a 3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one.

^b Disregard any impurity peak less than 0.03%.

SPECIFIC TESTS**Delete the following:**

- **MELTING RANGE OR TEMPERATURE** (741):
110°–112.5° ■^{1S} (USP36)
- **LOSS ON DRYING** (731)
Analysis: Dry a sample at 60° for 2 h.
Acceptance criteria: NMT 1.0%

Delete the following:

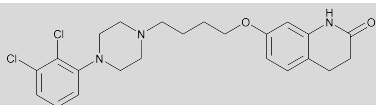
- **COMPLETENESS AND COLOR OF SOLUTION:** It is completely soluble in its own weight of cold water, the solution being colorless or NMT slightly yellow when viewed transversely in a tube having a diameter of 20 mm. ■^{1S} (USP36)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

- **USP REFERENCE STANDARDS** (11)
USP Antipyrine RS
■ USP Antipyrine Related Compound A RS
3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one.
C₁₀H₁₀N₂O 174.20 ■^{1S} (USP36)

Add the following:**Aripiprazole**

$C_{23}H_{27}Cl_2N_3O_2$ 448.39
 2(1*H*)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-;
 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl [129722-12-9].

DEFINITION

Aripiprazole contains NLT 98.0% and NMT 102.0% of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$), calculated on the dried basis.

IDENTIFICATION

- A. INFRARED ABSORPTION** (197K)
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**PROCEDURE**

Protect the solutions from light.

Diluent: Acetonitrile, methanol, water, and acetic acid (30:10:60:1)

Solution A: Acetonitrile and 0.05% trifluoroacetic acid (10:90)

Solution B: Acetonitrile and 0.05% trifluoroacetic acid (90:10)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
2	80	20
10	65	35
20	10	90
25	10	90
26	80	20
35	80	20

[NOTE—The gradient was established on an HPLC system with a dwell volume of approximately 650 μ L. The injection time can be adjusted relative to the start of a run to accommodate changes in dwell volume from one HPLC system to another to achieve the separation described.]

System suitability solution: 1 μ g/mL each of USP Aripiprazole RS and USP Aripiprazole Related Compound F RS in *Diluent*

Standard solution: 0.1 mg/mL of USP Aripiprazole RS in *Diluent*

Sample solution: 0.1 mg/mL of Aripiprazole in *Diluent*

Chromatographic system (See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm \times 10-cm; 3- μ m packing L1

Flow rate: 1.2 mL/min

Injection volume: 20 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for aripiprazole and aripiprazole related compound F are 1.0 and 1.1, respectively.]

Suitability requirements

Resolution: NLT 2.0 between aripiprazole and aripiprazole related compound F, *System suitability solution*

Tailing factor: NMT 1.5 for aripiprazole, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) in the portion of the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Aripiprazole RS in the *Standard solution* (mg/mL)

C_U = concentration of Aripiprazole in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **RESIDUE ON IGNITION** (281): NMT 0.1%

• **HEAVY METALS, Method II** (231): NMT 10 ppm

ORGANIC IMPURITIES

Protect the solutions from light.

Diluent, Solution A, Solution B, Mobile phase, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the *Assay*.

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Aripiprazole taken:

$$\text{Result} = (r_i/r_U) \times (1/F) \times 100$$

r_i = peak response of each impurity from the *Sample solution*

r_U = peak response of aripiprazole from the *Sample solution*

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Aripiprazole related compound G ^a	0.9	0.72	0.10
Aripiprazole	1.0	—	—
Aripiprazole related compound F ^b	1.1	—	—
Aripiprazole 4,4'-dimer ^c	1.3	1.0	0.10
Any other individual impurity	—	1.0	0.10
Total impurities	—	—	0.50

^a 7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]quinolin-2(1*H*)-one.

^b For system suitability and identification purposes only.

^c 1,1'-(Ethane-1,1-diyl)bis(2,3-dichloro-4-[4-[3,4-dihydroquinolin-2(1*H*)-one-7-yl]oxybutyl]piperazin-1-yl)benzene).

SPECIFIC TESTS**LOSS ON DRYING** (731)

Analysis: Dry at 105° for 3 h.

Acceptance criteria: NMT 0.3%

ADDITIONAL REQUIREMENTS

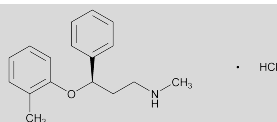
- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS** <11>

USP Aripiprazole RS
USP Aripiprazole Related Compound F RS
4-(2,3-Dichlorophenyl)-1-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)butyl]piperazin 1-oxide.
 $C_{23}H_{27}Cl_2N_3O_3$ 464.38₁₅ (USP36)

Add the following:

Atomoxetine Hydrochloride



$C_{17}H_{21}NO \cdot HCl$ 291.82
Benzenepropanamine, *N*-methyl- γ -(2-methylphenoxy)-, hydrochloride (–);
(–)-*N*-Methyl-3-phenyl-3-(*o*-tolylloxy)propylamine hydrochloride [82248-59-7].

DEFINITION

Atomoxetine Hydrochloride contains NLT 98.0% and NMT 102.0% of atomoxetine hydrochloride ($C_{17}H_{21}NO \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** <197K>
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the atomoxetine *R*-isomer from the *System suitability solution*, as obtained in the test for *Organic Impurities, Procedure 2*.
- **C. IDENTIFICATION TESTS—GENERAL, Chloride** <191>: Meets the requirements of the silver nitrate precipitate test

ASSAY

• PROCEDURE

Buffer: 2.9 g/L of phosphoric acid in water. Adjust with 5 M potassium hydroxide solution to a pH of 2.5. To 1 L of this solution add 5.9 g of octanesulfonic acid sodium salt monohydrate.

Mobile phase: *n*-Propanol and *Buffer* (27:73). [NOTE—The ratio of *n*-propanol in *Buffer* can be varied between 26:74 and 29:71 to meet system suitability requirements.]

System suitability solution: 0.1 mg/mL of USP Mandelic Acid RS, 0.15 mg/mL of USP Atomoxetine Related Compound A RS, and 0.25 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*

Standard solution: 0.25 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*. Sonication may be used to aid in dissolution.

Sample solution: 0.25 mg/mL of Atomoxetine Hydrochloride in *Mobile phase*. Sonication may be used to aid in dissolution.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm \times 15-cm; 3.5- μ m packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 μ L

Run time: 1.3 times the retention time of atomoxetine

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 1* in *Organic Impurities, Procedure 1* for relative retention times.]

Suitability requirements

Resolution: NLT 5.0 between mandelic acid and atomoxetine related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for atomoxetine, *System suitability solution*

Relative standard deviation: NMT 0.73% for atomoxetine, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of atomoxetine hydrochloride ($C_{17}H_{21}NO \cdot HCl$) in the portion of Atomoxetine Hydrochloride taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response from the *Sample solution*

r_s = peak response from the *Standard solution*

C_s = concentration of USP Atomoxetine Hydrochloride RS in the *Standard solution* (mg/mL)

C_u = concentration of Atomoxetine Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** <281>: NMT 0.1%

- **HEAVY METALS, Method II** <231>: NMT 10 ppm

[NOTE—It is required to perform *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2*.]

• ORGANIC IMPURITIES, PROCEDURE 1

Buffer and Mobile phase: Prepare as directed in the *Assay*.

System suitability solution: 0.10 mg/mL of USP Mandelic Acid RS, 0.15 mg/mL of USP Atomoxetine Related Compound A RS, and 0.25 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*

Standard solution: 0.0025 mg/mL of USP Atomoxetine Hydrochloride RS in *Mobile phase*

Sample solution: 2.5 mg/mL of Atomoxetine Hydrochloride in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*, except to use a run time of 2.6 times the retention time of atomoxetine.

System suitability

[NOTE—See *Table 1* for relative retention times.]

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 5.0 between mandelic acid and atomoxetine related compound A, *System suitability solution*

Tailing factor: NMT 1.5 for atomoxetine, *System suitability solution*

Relative standard deviation: NMT 5% from three injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of any individual impurity in the portion of Atomoxetine Hydrochloride taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response of each individual impurity from the *Sample solution*

r_s = peak response of atomoxetine from the *Standard solution*

C_s = concentration of USP Atomoxetine Hydrochloride RS in the *Standard solution* (mg/mL)

C_u = concentration of Atomoxetine Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See Table 1.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Mandelic acid ^a	0.20	—
Atomoxetine related compound A ^a	0.27	—
Desmethyl atomoxetine ^b	0.73	0.3
Atomoxetine	1.0	—
Any individual unspecified impurity	—	0.10
Total impurities	—	0.5

^a For system suitability purposes only.^b (R)-N-Methyl-3-phenoxy-3-phenylpropan-1-amine.**• ORGANIC IMPURITIES, PROCEDURE 2****Mobile phase:** Isopropyl alcohol, diethylamine, trifluoroacetic acid, and *n*-hexane (150: 1.5: 2.0: 846.5)**System suitability solution:** 3.5 mg/mL of USP Atomoxetine Hydrochloride RS, 17.5 µg/mL of USP Atomoxetine *S*-isomer RS, and 3.5 µg/mL of USP Atomoxetine Related Compound B RS, prepared by first dissolving the Reference Standards in ethanol, using 25% of final volume. Dilute with *n*-hexane to volume.**Sample solution:** 3.5 mg/mL of Atomoxetine Hydrochloride prepared by first dissolving it in ethanol, using 25% of final volume. Dilute with *n*-hexane to volume.**Chromatographic system**

(See Chromatography <621>, System Suitability.)

Mode: LC**Detector:** UV 273 nm**Column:** 4.6-mm × 25-cm; 5-µm packing L40**Flow rate:** 1 mL/min**Injection volume:** 10 µL**Run time:** 1.3 times the retention time of atomoxetine**System suitability****Sample:** System suitability solution

[NOTE—See Table 2 for relative retention times.]

Suitability requirements**Resolution:** NLT 1.75 between atomoxetine *S*-isomer and atomoxetine related compound B**Tailing factor:** NMT 1.8 for atomoxetine**Analysis****Sample:** Sample solutionCalculate the percentage of atomoxetine related compound B, atomoxetine related compound C, and atomoxetine *S*-isomer in the portion of Atomoxetine Hydrochloride taken:

$$\text{Result} = (r_u/r_t) \times 100$$

 r_u = peak response of each individual impurity from the Sample solution r_t = sum of all the peak responses of atomoxetine related compound B, atomoxetine related compound C, atomoxetine *S*-isomer, and atomoxetine from the Sample solution

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Atomoxetine <i>S</i> -isomer ^a	0.47	0.5
Atomoxetine related compound C ^b	0.52	0.1

^a N-Methyl-3-phenyl-3-(*o*-tolylxy)propan-1-amine.^b N-Methyl-3-phenyl-3-(*p*-tolylxy)propan-1-amine.

Table 2 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Atomoxetine related compound B	0.56	0.1
Atomoxetine	1.0	—

^a N-Methyl-3-phenyl-3-(*o*-tolylxy)propan-1-amine.^b N-Methyl-3-phenyl-3-(*p*-tolylxy)propan-1-amine.**SPECIFIC TESTS****• LOSS ON DRYING <731>****Analysis:** Dry a sample under vacuum at 105° for 2 h.**Acceptance criteria:** NMT 0.5%**ADDITIONAL REQUIREMENTS****• PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.**• USP REFERENCE STANDARDS <11>**

USP Atomoxetine Hydrochloride RS

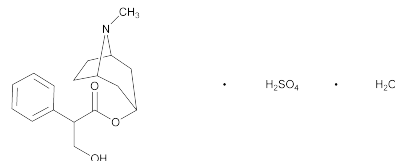
USP Atomoxetine Related Compound A RS
3-(Methylamino)-1-phenylpropan-1-ol.C₁₀H₁₅NO 165.23

USP Atomoxetine Related Compound B RS

N-Methyl-3-phenyl-3-(*m*-tolylxy)propan-1-amine hydrochloride.C₁₇H₂₁NO · HCl 291.82USP Atomoxetine *S*-isomer RS(S)-N-Methyl-3-phenyl-3-(*o*-tolylxy)propan-1-amine hydrochloride.C₁₇H₂₁NO · HCl 291.82

USP Mandelic Acid RS

α-Hydroxyphenylacetic acid.

C₈H₈O₃ 152.15[■]₁₅ (USP36)**Atropine Sulfate**(C₁₇H₂₃NO₃)₂ · H₂SO₄ · H₂O 694.83(C₁₇H₂₃NO₃)₂ · H₂SO₄ 676.83Benzeneacetic acid, α-(hydroxymethyl)-, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, *endo*-(±)-, sulfate (2:1) (salt), monohydrate;

1αH,5αH-Tropan-3-α-ol (±)-tropate (ester), sulfate (2:1) (salt) monohydrate [5908-99-6].

Anhydrous [55-48-1].

DEFINITION**Change to read:**Atropine Sulfate contains [■]NLT 98.0% and NMT 102.0% of atropine sulfate[■]₁₅ (USP36) (C₁₇H₂₃NO₃ · H₂SO₄), calculated on the anhydrous basis.**[CAUTION—**Handle Atropine Sulfate with exceptional care, because it is highly potent.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** <197K>
- **B. IDENTIFICATION TESTS—GENERAL**, Sulfate <191>
Sample solution: 50 mg/mL
Acceptance criteria: Meets the requirements

Add the following:

- **C.** The retention time of the atropine peak in the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the Assay. ^{1S (USP36)}

ASSAY**Change to read:**• **PROCEDURE**

■ **Buffer:** 1.8 g/L of monobasic potassium phosphate and 2.5 g/L of sodium 1-pentanesulfonate monohydrate, adjusted with phosphoric acid to a pH of 2.5
Diluent: Acetonitrile and Buffer (20:80)
Solution A: Acetonitrile and Buffer (5:95)
Solution B: Acetonitrile and Buffer (80:20)
Mobile phase: See Table 1.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	92	8
11	79	21
15	46	54
15.1	92	8
20	92	8

[NOTE—The gradient was established on an HPLC system with a dwell volume of approximately 0.8 mL. The injection time can be adjusted relative to the start of a run to accommodate changes in dwell volume from one HPLC system to another to achieve the separation described.]

System suitability solution: 1 µg/mL of USP Hyoscyamine Related Compound A RS and 0.5 mg/mL of USP Atropine Sulfate RS in *Diluent*

Sensitivity solution: 0.25 µg/mL of USP Atropine Sulfate RS in *Diluent*

Sample solution: 0.5 mg/mL of Atropine Sulfate in *Diluent*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 5 µL

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

Suitability requirements

[NOTE—See Table 2 for the relative retention times.]

Resolution: NLT 1.4 between hyoscyamine related compound A and atropine, *System suitability solution*

Tailing factor: 0.8–1.8 for atropine, *System suitability solution*

Signal-to-noise ratio: NLT 10 for atropine, *Sensitivity solution*

Relative standard deviation: NMT 1.0 for atropine, *System suitability solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of atropine sulfate ($C_{17}H_{23}NO_{32} \cdot H_2SO_4$) in the portion of Atropine Sulfate taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of atropine from the *Sample solution*

r_T = sum of the responses of all the peaks from the *Sample solution*

Acceptance criteria: NLT 98.0% and NMT 102.0% on the anhydrous basis. ^{1S (USP36)}

IMPURITIES

- **RESIDUE ON IGNITION** <281>: NMT 0.2%

Change to read:• **ORGANIC IMPURITIES**

Buffer, Diluent, Solution A, Solution B, Mobile phase, System suitability solution, Sensitivity solution, Sample solution, Chromatographic system, System suitability, and Suitability requirements: Proceed as directed in the Assay.

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Atropine Sulfate taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_T = sum of the responses of all the peaks from the *Sample solution*

F = relative response factor for each impurity (see Table 2)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tropic acid ^a	0.56	2.1	0.2
7-Hydroxyhyoscyamine ^b	0.66	1.0	0.2
Scopolamine ^c	0.72	1.0	0.2
6-Hydroxyhyoscyamine ^d	0.75	1.0	0.2
Hyoscyamine related compound A	0.97	1.2	0.3
Atropine	1.0	1.0	—
Littorine ^e	1.13	1.2	0.2
Apoatropine ^f	1.60	2.0	0.2

^a 3-Hydroxy-2-phenylpropanoic acid; also known as (2R,3S)-3-hydroxy-2-phenylpropanoic acid.

^b (1S,3R,5S)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (S)-3-hydroxy-2-phenylpropanoate; also known as (1S,3R,5S,6R)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2S)-3-hydroxy-2-phenylpropanoate.

^c (S)-(1R,2R,4S,5S,7S)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonan-7-yl 3-hydroxy-2-phenylpropanoate; also known as (S)-(1R,2R,4S,5S,7S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl (2S)-3-hydroxy-2-phenylpropanoate.

^d (1R,3S,5R)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (S)-3-hydroxy-2-phenylpropanoate; also known as (1R,3S,5R,6R)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2S)-3-hydroxy-2-phenylpropanoate.

^e (1R,3R,5S)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-hydroxy-3-phenylpropanoate; also known as (1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2R,3S)-2-hydroxy-3-phenylpropanoate.

^f (1R,3R,5S)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenylacrylate; also known as (1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylpropanoate.

Table 2 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.5

^a 3-Hydroxy-2-phenylpropanoic acid; also known as (2*R*,*S*)-3-hydroxy-2-phenylpropanoic acid.

^b (1*S*,3*R*,5*S*)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (5*S*)-3-hydroxy-2-phenylpropanoate; also known as (1*S*,3*R*,5*S*,6*R*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate.

^c (5*S*)-(1*R*,2*R*,4*S*,5*S*,7*S*)-9-Methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonan-7-yl 3-hydroxy-2-phenylpropanoate; also known as (5*S*)-(1*R*,2*R*,4*S*,5*S*,7*S*)-9-methyl-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]non-7-yl (2*S*)-3-hydroxy-2-phenylpropanoate.

^d (1*R*,3*S*,5*R*)-6-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl (5*S*)-3-hydroxy-2-phenylpropanoate; also known as (1*R*,3*S*,5*R*,6*R*)-6-hydroxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*S*)-3-hydroxy-2-phenylpropanoate.

^e (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-hydroxy-3-phenylpropanoate; also known as (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl (2*R*,*S*)-2-hydroxy-3-phenylpropanoate.

^f (1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 2-phenylacrylate; also known as (1*R*,3*r*,5*S*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 2-phenylpropanoate.

■_{1S} (USP36)

SPECIFIC TESTS

Delete the following:

- **MELTING RANGE OR TEMPERATURE, Class Ia (741):** Not lower than 187°, determined after drying at 120° for 4 h [NOTE—Because anhydrous Atropine Sulfate is hygroscopic, determine its melting temperature promptly on a specimen placed in the capillary tube immediately after drying.]■_{1S} (USP36)

Delete the following:

- **OPTICAL ROTATION, Angular Rotation (781A):** The observed rotation, in degrees, multiplied by 200, and divided by the length, in mm, of the polarimeter tube used, is between −0.60° and +0.05° (limit of hyoscyamine).
Sample solution: 1 g, in water to make a volume of 20 mL at 25°■_{1S} (USP36)

Add the following:

- **OPTICAL ROTATION, Specific Rotation (781)**
Sample solution: 0.1 mg/mL in water
Acceptance criteria: Between −0.50° and +0.05°■_{1S} (USP36)

Delete the following:

- **ACIDITY**
Sample solution: 0.05 mg/mL of Atropine Sulfate in water
Titrant: 0.020 N sodium hydroxide
Analysis: To 20 mL of *Sample solution*, and add 1 drop of *Methyl Red TS*. Titrate with *Titrant*.
Acceptance criteria: NMT 0.30 mL of *Titrant* is required to produce a yellow color.■_{1S} (USP36)

- **WATER DETERMINATION, Method I (921):** NMT 4.0%

ADDITIONAL REQUIREMENTS

Change to read:

- **PACKAGING AND STORAGE:** Preserve in tight, ■light-resistant■_{1S} (USP36) containers.

Change to read:

- **USP REFERENCE STANDARDS (11)**
USP Atropine Sulfate RS
■USP Hyoscyamine Related Compound A RS
Norhyoscyamine sulfate; (1*R*,3*r*,5*S*)-8-azabicyclo[3.2.1]oct-3-yl(2*S*)-3-hydroxy-2-phenylpropanoate.
C₁₆H₂₁NO₃ 275.34■_{1S} (USP36)

Atropine Sulfate Injection

DEFINITION

Atropine Sulfate Injection is a sterile solution of Atropine Sulfate in Water for Injection. It contains NLT 93.0% and NMT 107.0% of the labeled amount of atropine sulfate monohydrate [(C₁₇H₂₃NO₃)₂ · H₂SO₄ · H₂O].

IDENTIFICATION

Delete the following:

- **THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST (201)**
Adsorbent: Chromatographic silica gel
Sample solution: Use undiluted
Application volume: 15 µL
Spray reagent: Potassium iodoplatinate TS
Developing solvent system: Chloroform and diethylamine (9:1)
Analysis: Proceed as directed in the chapter, the spots on the plate located by spraying with *Spray reagent*.
Acceptance criteria: Meets the requirements.■_{1S} (USP36)

Add the following:

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.■_{1S} (USP36)

ASSAY

Change to read:

- **PROCEDURE**
■**Buffer:** Dissolve 4.1 g of sodium acetate and 2.9 mL of glacial acetic acid in 1 L of water.■_{1S} (USP36)
■**Mobile phase:** Transfer 5.1 g of tetrabutylammonium hydrogen sulfate to a 1-L volumetric flask. Add 50 mL of acetonitrile, and dilute with *Buffer* to volume. Adjust with 5 N sodium hydroxide to a pH of ■5.5.■_{1S} (USP36)
■**System suitability solution:** ■0.5 µg/mL of *p*-hydroxybenzoic acid and 64 µg/mL of USP Atropine Sulfate RS in water.■_{1S} (USP36)

Standard solution: 80 µg/mL of USP Atropine Sulfate RS

Sample solution: Nominally equivalent to 80 µg/mL of atropine sulfate in water, from a volume of the Injection containing an amount equivalent to 2 mg of atropine sulfate

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 30-cm × 3.9-mm; packing L1

Flow rate: 2 mL/min

Injection volume: 100 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times of atropine and *p*-hydroxybenzoic acid are 1.0 and 1.6, respectively.]

Suitability requirements

Resolution: NLT 2.2 between *p*-hydroxybenzoic acid and atropine, *System suitability solution*

Relative standard deviation: NMT 1.5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atropine sulfate monohydrate [(C₁₇H₂₃NO₃)₂ · H₂SO₄ · H₂O] in the portion of the Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Atropine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of atropine sulfate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of atropine sulfate monohydrate, 694.85

M_{r2} = molecular weight of anhydrous atropine sulfate, 676.83

Acceptance criteria: 93.0%–107.0%

SPECIFIC TESTS

• **pH** <791>: 3.0–6.5

• **BACTERIAL ENDOTOXINS TEST** <85>: NMT 55.6 USP Endotoxin Units/mg of atropine sulfate

• **OTHER REQUIREMENTS:** Meets the requirements in *Injections* <1>

ADDITIONAL REQUIREMENTS

Change to read:

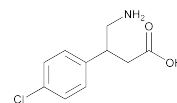
• **PACKAGING AND STORAGE:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass. ■Store at controlled room temperature. ■1S (USP36)

• **USP REFERENCE STANDARDS** <11>

USP Atropine Sulfate RS

USP Endotoxin RS

Baclofen



C₁₀H₁₂ClNO₂

213.66

Butanoic acid, 4-amino-3-(4-chlorophenyl)-;

β-(Aminomethyl)-*p*-chlorohydrocinnamic acid [1134-47-0].

DEFINITION

Change to read:

Baclofen contains ■NLT 98.0% and NMT 102.0% ■1S (USP36) of baclofen (C₁₀H₁₂ClNO₂), calculated on the anhydrous basis.

IDENTIFICATION

• A. INFRARED ABSORPTION <197M>

Add the following:

- **B.** The retention time of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■1S (USP36)

ASSAY

Delete the following:

• PROCEDURE

Sample solution: Dissolve 200 mg of Baclofen in a suitable volume of glacial acetic acid, sufficient to immerse the electrodes.

Analysis: Titrate the *Sample solution* with 0.1 N perchloric acid VS, using a calomel electrode containing a saturated solution of lithium chloride in glacial acetic acid. Perform a blank determination, and make any necessary correction (see *Titrimetry* <541>). Each mL of 0.1 N perchloric acid is equivalent to 21.37 mg of baclofen (C₁₀H₁₂ClNO₂).

Acceptance criteria: 99.0%–101.0% on the anhydrous basis. ■1S (USP36)

Add the following:

• PROCEDURE

Solution A: Dissolve 1.38 g of potassium dihydrogen phosphate and 1.74 g of sodium-1-pentanesulfonate in 1 L of water. Adjust with dilute phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile and methanol (1:1)

Diluent: *Solution A* and *Solution B* (65:35)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	65	35
5	65	35
15	45	55
25	45	55
27	65	35
30	65	35

Standard solution: 0.2 mg/mL of USP Baclofen RS in *Diluent*

Sample solution: 0.2 mg/mL of Baclofen in *Diluent*
Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 250-cm; 5-μm packing L1

Column temperature: 35°

Flow rate: 0.8 mL/min

Injection volume: 10 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of baclofen (C₁₀H₁₂ClNO₂) in the portion of the Baclofen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Baclofen RS in the *Standard solution* (mg/mL)

C_U = concentration of Baclofen in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis ■1S (USP36)

IMPURITIES

• **RESIDUE ON IGNITION** (281): NMT 0.3%

• **HEAVY METALS**, *Method II* (231): NMT 10 ppm

Change to read:

• ORGANIC IMPURITIES

■ **Solution A, Solution B, Diluent, Mobile phase, and Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.0015 mg/mL of USP Baclofen RS and 0.003 mg/mL of USP Baclofen Related Compound A RS in *Diluent*

Sample solution: 0.3 mg/mL of Baclofen in *Diluent*

System suitability

Sample: *Standard solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Tailing factor: NMT 1.5 for baclofen

Relative standard deviation: NMT 5.0% for both baclofen and baclofen related compound A

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of baclofen related compound A in the portion of the Baclofen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of baclofen related compound A from the *Sample solution*

r_S = peak response of baclofen related compound A from the *Standard solution*

C_S = concentration of USP Baclofen Related Compound A RS in the *Standard solution* (mg/mL)

C_U = concentration of Baclofen in the *Sample solution* (mg/mL)

Calculate the percentage of any unspecified impurity in the portion of the Baclofen taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of any unspecified impurity from the *Sample solution*

r_S = peak response of baclofen from the *Standard solution*

C_S = concentration of USP Baclofen RS in the *Standard solution* (mg/mL)

C_U = concentration of Baclofen in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Baclofen	1.0	—
Baclofen related compound A	2.3	1.0
Any individual unspecified impurity	—	0.10
Total impurities	—	2.0

■1S (USP36)

SPECIFIC TESTS

• **WATER DETERMINATION**, *Method I* (921): NMT 3.0%

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight containers.

■ Store at room temperature. ■1S (USP36)

• **USP REFERENCE STANDARDS** (11)

USP Baclofen RS

USP Baclofen Related Compound A RS

■ 4-(4-Chlorophenyl)-2-pyrrolidinone.

C₁₀H₁₀ClNO 195.65 ■1S (USP36)

Baclofen Tablets

DEFINITION

Baclofen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of baclofen (C₁₀H₁₂ClNO₂).

IDENTIFICATION

Delete the following:

• A.

Standard solution: 5 mg/mL of USP Baclofen RS in dehydrated alcohol and glacial acetic acid (4:1)

Sample solution: Equivalent to 5 mg/mL of baclofen from powdered Tablets in dehydrated alcohol and glacial acetic acid (4:1). [NOTE—Shake for 30 min and centrifuge.]

Chromatographic system

(See *Chromatography* (621), *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 20 μL

Developing solvent system: Butyl alcohol, glacial acetic acid, and water (4:1:1)

Spray reagent: 0.4 g of ninhydrin in 95 mL of butyl alcohol mixed with 5 mL of dilute glacial acetic acid (1 in 10)

Analysis: Develop the chromatogram until the solvent front has moved about three-fourths the length of the plate. Remove the plate from the developing chamber, and dry under a current of warm air. Spray the plate with the *Spray reagent* until the plate is slightly wet.

Place the plate in an oven maintained at 100° for 10 min.

Acceptance criteria: The R_f value of the principal orange-red spot of the *Sample solution* corresponds to that of the *Standard solution*. \blacksquare_{1S} (USP36)

Change to read:

- $\blacksquare_{A,1S}$ (USP36) The retention time of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

Change to read:

PROCEDURE

Diluent: Methanol, water, and glacial acetic acid (30:66:4)

Mobile phase: Methanol, 0.3 N acetic acid, and 0.36 N sodium 1-pentanesulfonate (44:55:2)

Standard solution: 4 mg/mL of USP Baclofen RS in *Diluent*

Sample solution: Weigh and finely powder NLT 20 Tablets. Transfer an amount equivalent to 40 mg to a 50-mL flask. Add 10.0 mL of *Diluent* to the flask. Sonicate to disperse, and shake by mechanical means for 30 min. Centrifuge a portion of this solution for 5 min, and filter.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 265 nm

Column: 3.9-mm × 30-cm; $\blacksquare_{10-\mu m,1S}$ (USP36) packing L1

Flow rate: 0.6 mL/min

Injection volume: 10 μ L

Run time: NLT 3 times the retention time of baclofen

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of labeled amount of baclofen ($C_{10}H_{12}ClNO_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Baclofen RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION, Procedure for a Pooled Sample** <711>
Medium: 0.01 N hydrochloric acid; 500 mL for Tablets containing NMT 10 mg of baclofen; 1000 mL for Tablets containing more than 10 mg of baclofen
Apparatus 2: 50 rpm
Time: 30 min
Mobile phase: Proceed as directed in the Assay.
Standard solution: USP Baclofen RS in *Medium*
Sample solution: Sample per *Dissolution* <711>.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 265 nm

Column: 3.9-mm × 30-cm; $\blacksquare_{10-\mu m,1S}$ (USP36) packing L1

Flow rate: 0.6 mL/min

Injection volume: 190 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of baclofen ($C_{10}H_{12}ClNO_2$) dissolved:

$$\blacksquare_{\text{Result}} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Baclofen RS in the *Standard solution* (mg/mL)

V = volume of *Medium*; 500 or 1000 mL

L = label claim (mg/Tablet)

\blacksquare_{1S} (USP36)

Tolerances: NLT 75% (Q) of the labeled amount of baclofen ($C_{10}H_{12}ClNO_2$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** <905>: Meet the requirements

IMPURITIES

Change to read:

ORGANIC IMPURITIES

Diluent, Mobile phase, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

Standard stock solution: 1 mg/mL of USP Baclofen Related Compound A RS in methanol

Standard solution: 0.16 mg/mL of USP Baclofen Related Compound A RS in *Diluent* from the *Standard stock solution*

Analysis

$\blacksquare_{\text{NOTE}}$ —The elution order is baclofen followed by baclofen related compound A. \blacksquare_{1S} (USP36)

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of baclofen related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area response from the *Sample solution*

r_S = peak area response from the *Standard solution*

C_S = concentration of USP Baclofen Related Compound A RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of baclofen in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 4.0%

ADDITIONAL REQUIREMENTS

Change to read:

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. $\blacksquare_{\text{Store}}$ at controlled room temperature. \blacksquare_{1S} (USP36)
- **USP REFERENCE STANDARDS** <11>
USP Baclofen RS
USP Baclofen Related Compound A RS
4-(4-Chlorophenyl)-2-pyrrolidinone.
 $C_{10}H_{10}ClNO$ 195.65

Benzethonium Chloride Concentrate

DEFINITION

Benzethonium Chloride Concentrate contains NLT 94.0% and NMT 106.0% of the labeled amount of benzethonium chloride ($C_{27}H_{42}ClNO_2$).

IDENTIFICATION

• A.

Sample: Evaporate a volume of the Concentrate, equivalent to 200 mg of benzethonium chloride, on a steam bath.

Analysis: To the residue add 2 mL of alcohol, 0.5 mL of 2 N nitric acid, and 1 mL of silver nitrate TS.

Acceptance criteria: A white precipitate, which is insoluble in 2 N nitric acid but soluble in 6 N ammonium hydroxide, is formed.

Delete the following:

• B.

Sample: Evaporate a volume of Concentrate, equivalent to 200 mg of benzethonium chloride, on a steam bath.

Acceptance criteria: The residue so obtained forms precipitates with 2 N nitric acid and with mercuric chloride TS, both of which dissolve upon the addition of alcohol. **■** USP36

Change to read:

• **B.** ■ USP36

Sample: Evaporate a volume of the Concentrate, equivalent to 200 mg of benzethonium chloride, on a steam bath.

Analysis: To the residue add 0.1 g of potassium nitrate, and heat on a steam bath for 3 min. Cautiously dilute the solution with water to 10 mL, add 0.5 g of granulated zinc, and warm the mixture for 10 min. Cool. Add 0.2 g of sodium nitrite to 1 mL of the clear liquid, and add this mixture to 20 mg of naphthol dipotassium disulfonate or naphthol disodium disulfonate in 1 mL of ammonium hydroxide.

Acceptance criteria: The solution turns orange-red, and a brown precipitate may be formed.

ASSAY

• PROCEDURE

Sample solution: Equivalent to 200 mg of benzethonium chloride from a volume of Concentrate, in a glass-stoppered flask

Analysis: Add 0.4 mL of bromophenol blue solution (1 in 2000), 10 mL of chloroform, and 1 mL of 1 N sodium hydroxide. Titrate with 0.02 M sodium tetraphenylboron VS until the blue color disappears from the chloroform layer. Add the last portions of the sodium tetraphenylboron solution dropwise, agitating vigorously after each addition. Each mL of 0.02 M sodium tetraphenylboron is equivalent to 8.962 mg of benzethonium chloride ($C_{27}H_{42}ClNO_2$).

Acceptance criteria: 94.0%–106.0% of the labeled amount of benzethonium chloride

IMPURITIES

• LIMIT OF NITRITES

Sample: One drop of Concentrate on a spot plate

Analysis: To the *Sample* add one drop each of glacial acetic acid, sulfanilic acid in acetic acid solution (1 in 100), and 1-naphthylamine-acetic acid solution (prepared by boiling 30 mg of 1-naphthylamine in 70 mL of water, decanting the colorless solution from the blue-violet residue, and mixing with 30 mL of glacial acetic acid).

Acceptance criteria: No red color develops in the resulting solution within 10 min.

SPECIFIC TESTS

• OXIDIZING SUBSTANCES

Sample: 5 mL

Analysis: To the *Sample* add 0.5 mL of potassium iodide TS and a few drops of 3 N hydrochloric acid.

Acceptance criteria: The solution does not acquire a yellow color.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at room temperature.

• **LABELING:** The label states that this article is not intended for direct administration to humans or animals.

Benzethonium Chloride Topical Solution

DEFINITION

Benzethonium Chloride Topical Solution contains NLT 95.0% and NMT 105.0% of the labeled amount of benzethonium chloride ($C_{27}H_{42}ClNO_2$).

IDENTIFICATION

• A.

Sample solution: Evaporate a volume of Topical Solution, equivalent to 200 mg of benzethonium chloride, on a steam bath.

Analysis: To the residue add 2 mL of alcohol, 0.5 mL of 2 N nitric acid, and 1 mL of silver nitrate TS.

Acceptance criteria: A white precipitate, which is insoluble in 2 N nitric acid but soluble in 6 N ammonium hydroxide, is formed.

Delete the following:

• B.

Sample solution: Evaporate a volume of Topical Solution, equivalent to 200 mg of benzethonium chloride, on a steam bath.

Acceptance criteria: The residue so obtained forms precipitates with 2 N nitric acid and with mercuric chloride TS, both of which dissolve upon the addition of alcohol. **■** USP36

Change to read:

• **B.** ■ USP36

Sample solution: Evaporate a volume of Topical Solution, equivalent to 200 mg of benzethonium chloride, on a steam bath.

Analysis: To the residue add 0.1 g of potassium nitrate, and heat on a steam bath for 3 min. Cautiously dilute the solution with water to 10 mL, add 0.5 g of granulated zinc, and warm the mixture for 10 min. Cool. Add 0.2 g of sodium nitrite to 1 mL of the clear liquid, and add this mixture to 20 mg of naphthol dipotassium disulfonate or naphthol disodium disulfonate in 1 mL of ammonium hydroxide.

Acceptance criteria: The solution turns orange-red, and a brown precipitate may be formed.

ASSAY

• PROCEDURE

Sample solution: Equivalent to 200 mg of benzethonium chloride from a volume of Topical Solution, in a glass-stoppered flask

Analysis: Add 0.4 mL of bromophenol blue solution (1 in 2000), 10 mL of chloroform, and 1 mL of 1 N so-

dium hydroxide. Titrate with 0.02 M sodium tetraphenylboron VS until the blue color disappears from the chloroform layer. Add the last portions of the sodium tetraphenylboron solution dropwise, agitating vigorously after each addition. Each mL of 0.02 M sodium tetraphenylboron is equivalent to 8.962 mg of benzethonium chloride ($C_{27}H_{42}ClNO_2$).

Acceptance criteria: 95.0%–105.0% of the labeled amount of benzethonium chloride

IMPURITIES

• ORGANIC IMPURITIES, LIMIT OF NITRITES

Sample: One drop of Topical Solution on a spot plate

Analysis: To the *Sample* add one drop each of glacial acetic acid, sulfanilic acid in acetic acid (1 in 100), and 1-naphthylamine–acetic acid solution (prepared by boiling 30 mg of 1-naphthylamine in 70 mL of water, decanting the colorless solution from the blue-violet residue, and mixing with 30 mL of glacial acetic acid).

Acceptance criteria: No red color develops in the resulting solution within 10 min.

SPECIFIC TESTS

• OXIDIZING SUBSTANCES

Sample: 5 mL

Analysis: To the *Sample* add 0.5 mL of potassium iodide TS and a few drops of 3 N hydrochloric acid.

Acceptance criteria: The solution does not acquire a yellow color.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Benzoyl Peroxide Lotion

DEFINITION

Benzoyl Peroxide Lotion is benzoyl peroxide in a suitable lotion base. It contains NLT 90.0% and NMT 110.0% of the labeled amount of benzoyl peroxide ($C_{14}H_{10}O_4$).

IDENTIFICATION

Delete the following:

• A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST (201)

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Standard solution: 10 mg/mL of Hydrous Benzoyl Peroxide, previously subjected to the *Assay*, in methanol

Sample solution: Equivalent to 10 mg/mL of benzoyl peroxide from Lotion in acetone

Application volume: 5 μ L

Developing solvent system: Toluene, dichloromethane, and glacial acetic acid (50:2:1)

Analysis

Samples: *Standard solution* and *Sample solution*
Place the plate in a developing chamber containing and equilibrated with *Developing solvent system*. Develop the chromatogram until the solvent front has moved three-fourths of the length of the plate. Remove the plate, and allow the solvent to evaporate. Observe the plate under short-wavelength UV light.

Acceptance criteria: The R_f value of the principal spot from the solution under test corresponds to that from the *Standard solution*. ■^{1S} (USP36)

Change to read:

- ■^{1S} (USP36) The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• PROCEDURE

Mobile phase: Acetonitrile in water (5 in 10)

Internal standard solution: 3.6 mg/mL of ethyl benzoate in acetonitrile

Standard stock solution: Transfer a suitable quantity of benzoyl peroxide, recently subjected to the *Assay* under *Hydrous Benzoyl Peroxide*, in a weighed conical flask fitted with a glass stopper. Weigh again to obtain the weight of the specimen, and quantitatively dissolve in acetonitrile to obtain a solution containing 0.8 mg/mL.

Standard solution: 10 mL of *Standard stock solution* and 5 mL of *Internal standard solution*. Dilute with acetonitrile to 25 mL.

This *Standard solution* contains 0.32 mg/mL of benzoyl peroxide.

Sample stock solution: Transfer the equivalent to 40 mg of benzoyl peroxide from Lotion in a 50-mL volumetric flask, and add 40 mL of acetonitrile. Shake vigorously until the material is thoroughly dispersed. Sonicate the mixture for 5 min, dilute with acetonitrile to volume, mix, and filter.

Sample solution: 10 mL of *Sample stock solution* and 5 mL of *Internal standard solution*. Dilute with acetonitrile to 25 mL.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm \times 30-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 10 μ L

System suitability

Sample: *Standard solution* (three replicate injections)
[NOTE—The retention times for ethyl benzoate and benzoyl peroxide are 7 and 14 min, respectively.]

Suitability requirements

Resolution: NLT 2.0 between ethyl benzoate and benzoyl peroxide

Tailing factor: NMT 2.0 for the ethyl benzoate and benzoyl peroxide peaks

Peak response ratios: The lowest and highest peak response ratios (R_s) agree within 2.0%.

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of benzoyl peroxide ($C_{14}H_{10}O_4$) in the portion of Lotion taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of benzoyl peroxide to ethyl benzoate from the *Sample solution*

R_S = peak response ratio of benzoyl peroxide to ethyl benzoate from the *Standard solution*

C_S = concentration of benzoyl peroxide in the *Standard solution* (mg/mL)

C_U = nominal concentration of benzoyl peroxide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• ORGANIC IMPURITIES

Solution A: Acetonitrile and glacial acetic acid (1000:1)

Solution B: Glacial acetic acid and water (1:1000)

Mobile phase: See Table 1.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	18	82
20	60	40
30	60	40

System suitability solution: 100 µg/mL of benzoic acid and 60 µg/mL of methylparaben in acetonitrile

Standard solution A: 500 µg/mL of benzoic acid in acetonitrile

Standard solution B: 20 µg/mL of ethyl benzoate in acetonitrile

Standard solution C: 20 µg/mL of benzaldehyde in acetonitrile

Standard solution D: Prepare a solution of hydrous benzoyl peroxide, previously subjected to the Assay under *Hydrous Benzoyl Peroxide*, in acetonitrile containing the equivalent of 40 µg/mL of anhydrous benzoyl peroxide.

Sample solution: Equivalent to 100 mg of benzoyl peroxide from Lotion. In a 50-mL volumetric flask add 25 mL of acetonitrile, and shake vigorously to disperse the specimen. Sonicate for 5 min, dilute with acetonitrile to volume, mix, and filter.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1.2 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between benzoic acid and methylparaben

Tailing factor: NMT 2.0 for the benzoic acid and methylparaben peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Acceptance criteria: The responses of any peaks from the *Sample solution* corresponding to benzoic acid, ethyl benzoate, and benzaldehyde are NMT those of the main peaks from *Standard solution A* (25%), *Standard solution B* (1%), and *Standard solution C* (1%), respectively. The response of any other impurity peak from the *Sample solution*, other than the main benzoyl peroxide peak, any benzoic acid, ethyl benzoate, benzaldehyde, methylparaben, or propylparaben peak, and any solvent peak, is NMT that from *Standard solution D* (2%); and the sum of the responses of all the impurity peaks, other than those of benzoic acid, ethyl benzoate, and benzaldehyde, is NMT that from *Standard solution D* (2%).

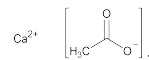
SPECIFIC TESTS

• **PH** <791>: 2.8–6.6

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

Calcium Acetate



C₄H₆CaO₄

158.17

Acetic acid, calcium salt;

Calcium acetate [62-54-4].

DEFINITION

Calcium Acetate contains NLT 99.0% and NMT 100.5% of calcium acetate (C₄H₆CaO₄), calculated on the anhydrous basis.

IDENTIFICATION

• **A. IDENTIFICATION TESTS—GENERAL,** *Calcium* <191> and *Acetate* <191>

Sample solution: 50 mg/mL

Acceptance criteria: Meets the requirements

ASSAY

• PROCEDURE

Sample: 300 mg

Analysis: Dissolve the *Sample* in 150 mL of water containing 2 mL of 3 N hydrochloric acid. While stirring, preferably with a magnetic stirrer, add about 30 mL of 0.05 M edetate disodium VS from a 50-mL buret. Add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue, and continue the titration to a blue endpoint. Each mL of 0.05 M edetate disodium is equivalent to 7.909 mg of calcium acetate (C₄H₆CaO₄).

Acceptance criteria: 99.0%–100.5% on the anhydrous basis

IMPURITIES

• **ARSENIC,** *Method I* <211>: NMT 3 ppm

• **CHLORIDE AND SULFATE,** *Chloride* <221>

Standard: 0.70 mL of 0.020 N hydrochloric acid

Sample: 1.0 g

Acceptance criteria: 0.05%

• **CHLORIDE AND SULFATE,** *Sulfate* <221>

Standard: 0.15 mL of 0.020 N sulfuric acid

Sample: 0.25 g

Acceptance criteria: 0.06%

• **HEAVY METALS,** *Method I* <231>

Test preparation: Dissolve 0.8 g of Calcium Acetate in 20 mL of water. Add 3.0 mL of glacial acetic acid, dilute with water to 25 mL, and adjust with glacial acetic acid to a pH of 3.8–4.0, measured with a pH meter.

Monitor preparation: Prepare as directed for the *Test preparation*, 2.0 mL of *Standard Lead Solution* being added.

Acceptance criteria: NMT 25 ppm

• **LEAD** <251>: NMT 10 ppm

• **LIMIT OF ALUMINUM**

[NOTE—Use where it is labeled as intended for parenteral use or for use in hemodialysis or peritoneal dialysis.]

Buffer: Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0, and dilute with water to 250 mL.

Aluminum standard solution: 1.0 µg/mL of aluminum. Prepare as directed for *Standard Preparations in Aluminum* <206>.

Standard solution: Prepare a solution containing 2.0 mL of *Aluminum standard solution*, 5 mL of *Buffer*, and 48 mL of water, and extract this solution with successive portions of 10, 10, and 5 mL of 0.5% 8-hydroxyquinoline in chloroform. Combine the chloroform extracts in a 50-mL volumetric flask. Dilute the combined extracts with chloroform to volume.

Sample solution: Dissolve 1.0 g of Calcium Acetate in 50 mL of water, and add 5 mL of *Buffer*. Extract this solution with successive portions of 10, 10, and 5 mL of

0.5% 8-hydroxyquinoline in chloroform. Combine the chloroform extracts in a 50-mL volumetric flask. Dilute the combined extracts with chloroform to volume.

Blank solution: Prepare a solution containing 50 mL of water and 5 mL of *Buffer*. Extract this solution with successive portions of 10, 10, and 5 mL of 0.5% 8-hydroxyquinoline in chloroform. Combine the chloroform extracts in a 50-mL volumetric flask. Dilute the combined extracts with chloroform to volume.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: Fluorescence

Excitation wavelength: 392 nm

Emission wavelength: 518 nm

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank solution*

Use the *Blank solution* to zero the instrument.

Acceptance criteria: 2 ppm; the fluorescence of the *Sample solution* is NMT that of the *Standard solution*.

• **LIMIT OF BARIUM**

[NOTE—Use where it is labeled as intended for use in hemodialysis or peritoneal dialysis.]

Barium chloride solution: 500 µg/mL of barium in water from anhydrous barium chloride

Buffer: Ammonium sulfate solution (1 in 10)

Standard solution: To a tube add 1 g of ammonium acetate, 2 mL of 1 N hydrochloric acid, 3.0 mL of *Barium chloride solution*, and sufficient water to bring the volume to 40 mL.

Sample stock solution: 250 mg/mL of Calcium Acetate and 25 mg/mL of ammonium acetate in 1 N hydrochloric acid. The pH of this solution is 4.5–5.5. Filter, and cover the solution.

Sample solutions: To four separate tubes add 1.0, 1.5, 2.0, and 2.5 mL of *Barium chloride solution*. To each tube add a sufficient volume of the *Sample stock solution* to bring the volume to 40 mL.

Analysis: To the *Sample solutions* and the *Standard solution* add, with brisk stirring, 3.0 mL of *Buffer*, and allow to stand for 20 min.

Acceptance criteria: The *Sample solutions* containing 1.0 and 1.5 mL of *Barium chloride solution* remain clear or are only faintly turbid. The *Sample solution* containing 2.0 mL of *Barium chloride solution* is not more turbid than the *Standard solution*.

• **LIMIT OF FLUORIDE**

[NOTE—Prepare and store all solutions in plastic containers.]

Buffer: 294 mg/mL of sodium citrate dihydrate in water

Standard stock solution: 1.11 mg/mL of USP Sodium Fluoride RS in water

Standard solution: Combine 20.0 mL of *Standard stock solution* with 50.0 mL of *Buffer*, and dilute with water to 100.0 mL. Equivalent to 100 µg/mL of fluoride

Sample solution: Transfer 2.0 g of Calcium Acetate to a beaker containing a plastic-coated stirring bar. Add 20.0 mL of water and 2.0 mL of hydrochloric acid, and stir until dissolved. Add 50.0 mL of *Buffer* and sufficient water to make 100 mL.

Electrode system: Use a fluoride-specific, ion-indicating electrode and a silver–silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see pH (791)).

Analysis

Samples: *Standard solution* and *Sample solution*

Transfer 50.0 mL of *Buffer* and 2.0 mL of hydrochloric acid to a beaker, and add water to make 100 mL. Add a plastic-coated stirring bar, insert the electrodes into the solution, stir for 15 min, and read the potential, in mV. Continue stirring, and at 5-min intervals add 100, 100, 300, and 500 µL of the *Standard solution*, reading the potential 5 min after each addition. Plot the loga-

ritms of the cumulative fluoride ion concentrations (0.1, 0.2, 0.5, and 1.0 µg/mL) versus potential, in mV. Rinse and dry the electrodes, insert them into the *Sample solution*, stir for 5 min, and read the potential, in mV. From the measured potential and the standard response line determine the concentration, *C*, in µg/mL, of fluoride ion in the *Sample solution*.

Calculate the amount of fluoride (ppm) in the sample taken by multiplying *C* by 50.

Acceptance criteria: 50 ppm

• **LIMIT OF MAGNESIUM**

[NOTE—Use where it is labeled as intended for use in hemodialysis or peritoneal dialysis. The *Standard solution* and the *Sample solutions* may be modified, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Standard stock solution: 1000 µg/mL of magnesium in 1 N nitric acid from magnesium oxide

Standard solution: 5.0 µg/mL of magnesium from the *Standard stock solution*

Sample solution: 2 mg/mL of Calcium Acetate

Linearity solution A: Dilute 20.0 mL of the *Sample solution* with water to 25.0 mL (0 µg/mL of magnesium).

Linearity solution B: Dilute 2.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (0.4 µg/mL of magnesium).

Linearity solution C: Dilute 4.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (0.8 µg/mL of magnesium).

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: Atomic absorption spectrophotometry

Analytical wavelength: 285.2 nm

Flame: Air–acetylene

Lamp: Magnesium hollow-cathode

Blank: Water

Analysis

Samples: *Linearity solutions A, B, and C*

Plot the absorbances of the *Linearity solutions* versus their content of magnesium (0, 0.4, and 0.8 µg/mL), draw the straight line best fitting the three points, and extrapolate the line until it intercepts the concentration axis. From the intercept determine the amount, in µg/mL, of magnesium in the *Sample solution*.

Calculate the percentage of magnesium in the sample by multiplying this value by 0.0625.

Acceptance criteria: NMT 0.05%

• **LIMIT OF NITRATE**

Sample solution: 100 mg/mL of Calcium Acetate in water

Analysis: To 10 mL of the *Sample solution* add 5 mg of sodium chloride, 0.05 mL of indigo carmine TS, and, with stirring, 10 mL of nitrogen-free sulfuric acid.

Acceptance criteria: The blue color persists for NLT 10 min.

• **LIMIT OF POTASSIUM**

[NOTE—Use where it is labeled as intended for use in hemodialysis or peritoneal dialysis. The *Standard solution* and *Sample solutions* may be modified, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Standard stock solution: 23.84 mg/mL of potassium chloride, using potassium chloride previously dried at 105° for 2 h, equivalent to 12.5 mg/mL of potassium

Standard solution: 31.25 µg/mL of potassium from the *Standard stock solution*

Sample solution: 12.5 mg/mL of Calcium Acetate

Linearity solution A: Dilute 20.0 mL of the *Sample solution* with water to 25.0 mL (0 µg/mL of potassium).

Linearity solution B: Dilute 2.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (2.5 µg/mL of potassium).

Linearity solution C: Dilute 4.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (5.0 µg/mL of potassium).

Instrumental conditions(See *Spectrophotometry and Light-Scattering* (851).)**Mode:** Atomic absorption spectrophotometry**Analytical wavelength:** 766.7 nm**Lamp:** Potassium hollow-cathode**Flame:** Air–acetylene**Blank:** Water**Analysis****Samples:** *Linearity solutions A, B, and C*

Plot the absorbances of the *Linearity solutions* versus their content of potassium (0, 2.5, and 5.0 µg/mL), draw the straight line best fitting the three points, and extrapolate the line until it intercepts the concentration axis. From the intercept determine the amount, in µg/mL, of potassium in the *Sample solution*.

Calculate the percentage of potassium in the sample by multiplying this value by 0.01.

Acceptance criteria: NMT 0.05%• **LIMIT OF SODIUM**

[NOTE—Use where it is labeled as intended for use in hemodialysis or peritoneal dialysis. The *Standard solution* and the *Sample solutions* may be modified, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Standard stock solution: 25.42 mg/mL of sodium chloride, using sodium chloride previously dried at 105° for 2 h, equivalent to 10.0 mg/mL of sodium

Standard solution: 250 µg/mL of sodium from the *Standard stock solution*

Sample solution: 10 mg/mL of Calcium Acetate

Linearity solution A: Dilute 20.0 mL of the *Sample solution* with water to 25.0 mL (0 µg/mL of sodium).

Linearity solution B: Dilute 2.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (20 µg/mL of sodium).

Linearity solution C: Dilute 4.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (40 µg/mL of sodium).

Instrumental conditions(See *Spectrophotometry and Light-Scattering* (851).)**Mode:** Atomic absorption spectrophotometry**Analytical wavelength:** 589.0 nm**Lamp:** Sodium hollow-cathode**Flame:** Air–acetylene**Blank:** Water**Analysis****Samples:** *Linearity solutions A, B, and C*

Plot the absorbances of the *Linearity solutions* versus their content of sodium (0, 20, and 40 µg/mL), draw the straight line best fitting the three points, and extrapolate the line until it intercepts the concentration axis. From the intercept determine the amount, in µg/mL, of sodium in the *Sample solution*.

Calculate the percentage of sodium in the sample by multiplying this value by 0.0125.

Acceptance criteria: NMT 0.5%• **LIMIT OF STRONTIUM**

[NOTE—Use where it is labeled as intended for use in hemodialysis or peritoneal dialysis. The *Standard solution* and *Sample solutions* may be modified, if necessary, to obtain solutions of suitable concentrations, adaptable to the linear or working range of the instrument.]

Standard stock solution: 2.45 mg/mL of strontium acetate in water, equivalent to 1000 µg/mL of strontium

Standard solution: 50.0 µg/mL of strontium from the *Standard stock solution*

Sample solution: 20 mg/mL of Calcium Acetate

Linearity solution A: Dilute 20.0 mL of the *Sample solution* with water to 25.0 mL (0 µg/mL of strontium).

Linearity solution B: Dilute 2.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (4 µg/mL of strontium).

Linearity solution C: Dilute 4.0 mL of the *Standard solution* and 20.0 mL of the *Sample solution* with water to 25.0 mL (8 µg/mL of strontium).

Instrumental conditions(See *Spectrophotometry and Light-Scattering* (851).)**Mode:** Atomic absorption spectrophotometry**Analytical wavelength:** 460.7 nm**Lamp:** Strontium hollow-cathode**Flame:** Nitrous oxide–acetylene**Blank:** Water**Analysis****Samples:** *Linearity solutions A, B, and C*

Plot the absorbances of the *Linearity solutions* versus their content of strontium (0, 4, and 8 µg/mL), draw the straight line best fitting the three points, and extrapolate the line until it intercepts the concentration axis. From the intercept determine the amount, in µg/mL, of strontium in the *Sample solution*.

Calculate the percentage of strontium in the sample by multiplying this value by 0.00625.

Acceptance criteria: NMT 0.05%• **READILY OXIDIZABLE SUBSTANCES**

Sample solution: 20 mg/mL of Calcium Acetate in boiling water

Analysis: Add a few glass beads to 100 mL of the *Sample solution*, 6 mL of 10 N sulfuric acid, and 0.3 mL of 1 N potassium permanganate. Mix, boil gently for 5 min, and allow the precipitate to settle.

Acceptance criteria: The pink color in the supernatant is not completely discharged.

SPECIFIC TESTS• **pH** (791)

Sample solution: 50 mg/mL

Acceptance criteria: 6.3–9.6

Change to read:• **WATER DETERMINATION, Method I** (921)

Sample: 0.100 g_{NIS} (USP36)

Analysis: Proceed as directed in the chapter, adding 2 mL_{NIS} (USP36) of glacial acetic acid to the titration vessel in addition to the methanol.

Acceptance criteria: NMT 7.0%

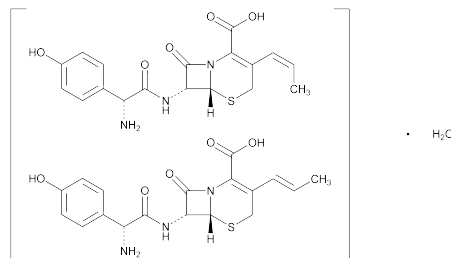
ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

• **LABELING:** Where Calcium Acetate is intended for use in hemodialysis or peritoneal dialysis, it is so labeled.

• **USP REFERENCE STANDARDS** (11)

USP Sodium Fluoride RS

Cefprozil

$C_{18}H_{19}N_3O_5S \cdot H_2O$

407.44

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-(1-propenyl)-, monohydrate, [6R-[6α,7β(R*)]];

(6*R*,7*R*)-7-[(*R*)-2-Amino-2-(*p*-hydroxyphenyl)acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate [121123-17-9].
Anhydrous 389.43
[92665-29-7].

DEFINITION

Cefprozil contains NLT 900 µg/mg and NMT 1050 µg/mg of cefprozil (C₁₈H₁₉N₃O₅S), calculated on the anhydrous basis.

IDENTIFICATION**Change to read:**

- A. INFRARED ABSORPTION** (197K)
Standard: ■ USP Cefprozil RS ■_{1S} (USP36)
- B.** The retention times of the cefprozil (Z)-isomer and cefprozil (E)-isomer peaks from the *Sample solution* correspond to those of the *Standard solutions*, as obtained in the *Assay*.

ASSAY**Change to read:**

- PROCEDURE**
Buffer: 11.5 g/L of monobasic ammonium phosphate in water. Adjust, if necessary, with phosphoric acid to a pH of 4.4.
Mobile phase: Acetonitrile and *Buffer* (100:900)
■_{1S} (USP36)
Standard solution 1: 0.25 mg/mL of USP Cefprozil (Z)-Isomer RS in water. Use this solution within 6 h.
Standard solution 2: 0.025 mg/mL of USP Cefprozil (E)-Isomer RS in water. Use this solution within 6 h.
System suitability solution: 0.125 mg/mL each of USP Cefprozil (Z)-Isomer RS and USP Cefprozil (E)-Isomer RS in water. Use this solution within 6 h.
Sample solution: 0.3 mg/mL of Cefprozil in water. Shake to dissolve. Use this solution within 6 h.
Chromatographic system
(See *Chromatography* (621), *System Suitability*).
Mode: LC
Detector: UV 280 nm
Column: ■ 4.6-mm × 30-cm; ■_{1S} (USP36) 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution 1*
[NOTE—The relative retention times for cefprozil (Z)-isomer and cefprozil (E)-isomer are about 0.7 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.5 between cefprozil (Z)-isomer and cefprozil (E)-isomer, *System suitability solution*
■_{1S} (USP36)
Tailing factor: 0.9–1.1, *Standard solution 1*
■_{1S} (USP36)
Relative standard deviation: NMT 2.0%, *Standard solution 1*
Analysis
Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*
Calculate the amount (µg) of cefprozil (Z)-isomer (C₁₈H₁₉N₃O₅S) in each mg of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

- r_U = peak response of cefprozil (Z)-isomer from the *Sample solution*
 r_S = peak response of cefprozil (Z)-isomer from *Standard solution 1*

- C_S = concentration of USP Cefprozil (Z)-isomer RS in *Standard solution 1* (mg/mL)
 C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)
 P = potency of USP Cefprozil (Z)-isomer RS (µg/mg)

Calculate the amount (µg) of cefprozil (E)-isomer (C₁₈H₁₉N₃O₅S) in each mg of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

- r_U = peak response of cefprozil (E)-isomer from the *Sample solution*
 r_S = peak response of cefprozil (E)-isomer from *Standard solution 2*
 C_S = concentration of USP Cefprozil (E)-isomer RS in *Standard solution 2* (mg/mL)
 C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)
 P = potency of USP Cefprozil (E)-isomer RS (µg/mg)
Calculate the quantity, in µg, of cefprozil (C₁₈H₁₉N₃O₅S) in each mg of the Cefprozil taken by adding the values, in µg/mg, of the cefprozil (Z)-isomer and the cefprozil (E)-isomer.

Acceptance criteria: 900–1050 µg/mg on the anhydrous basis

IMPURITIES**Add the following:****■ ORGANIC IMPURITIES, PROCEDURE 1**

Use *Organic Impurities, Procedure 1* when the impurity profile includes Z-cefprozil open ring, E-cefprozil open ring, and cefprozil related compound K.

Solution A: 11.5 g/L of monobasic ammonium phosphate in water. Adjust, if necessary, with phosphoric acid or ammonium hydroxide to a pH of 4.4.

Solution B: Acetonitrile and *Solution A* (1:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	81	19
8	81	19
20	36	64
25	36	64
27	81	19
30	81	19

[NOTE—These gradient elution times are established on an HPLC system with a dwell volume of approximately 1.3 mL. The gradient elution times in the table can be adjusted as necessary to achieve the separation described.]

Standard stock solution: 0.25 mg/mL each of USP Cefprozil (Z)-Isomer RS, USP Amoxicillin Related Compound I RS, and USP Cefprozil Related Compound D RS in a mixture of 1 M hydrochloric acid and *Solution A*. Prepare the solution as follows. Dissolve USP Amoxicillin Related Compound I RS, USP Cefprozil (Z)-Isomer RS, and USP Cefprozil Related Compound D RS in 1 M hydrochloric acid, using 20% of the final volume. Dilute with *Solution A* to volume.

Sensitivity solution: 2.5 µg/mL each of cefprozil (Z)-isomer, amoxicillin related compound I, and cefprozil related compound D in *Solution A* from *Standard stock solution*. Store the solution at 4°, and use within 8 h.
Standard solution: 50 µg/mL each of cefprozil (Z)-isomer, amoxicillin related compound I, and cefprozil re-

lated compound D in *Solution A* from the *Standard stock solution*. Store the solution at 4°, and use within 12 h.

Sample solution: 5 mg/mL of Cefprozil in a mixture of 1 M hydrochloric acid and *Solution A*, prepared as follows. Dissolve the Cefprozil first in 1 M hydrochloric acid using 4% of the final volume, and then dilute with *Solution A* to volume. Store the solution at 4°, and use within 3 h.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Autosampler temperature: 4°

Injection volume: 10 μL

System suitability

Samples: *Standard solution* and *Sensitivity solution*
USP Cefprozil Related Compound D RS contains the (Z)- and (E)-isomers of cefprozil related compound D. See Table 2 for relative retention times.

Suitability requirements

Resolution: NLT 1.4 between the (E)-isomer of cefprozil related compound D and cefprozil (Z)-isomer, *Standard solution*

Relative standard deviation: NMT 10.0% for cefprozil, amoxicillin related compound I, and each isomer of cefprozil related compound D, *Standard solution*

Signal-to-noise ratio: NLT 10 for cefprozil, amoxicillin related compound I, and each isomer of cefprozil related compound D, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amoxicillin related compound I in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = peak response of amoxicillin related compound I from the *Sample solution*

r_S = peak response of amoxicillin related compound I from the *Standard solution*

C_S = concentration of USP Amoxicillin Related Compound I RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of amoxicillin related compound I in USP Amoxicillin Related Compound I RS (mg/mg)

Calculate the percentage of cefprozil related compound D in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = sum of the responses for cefprozil related compound D (Z)-isomer and cefprozil related compound D (E)-isomer from the *Sample solution*

r_S = peak response of cefprozil related compound D (Z)-isomer from the *Standard solution*

C_S = concentration of USP Cefprozil Related Compound D RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of cefprozil related compound D (Z)-isomer in USP Cefprozil Related Compound D RS (mg/mg)

Calculate the percentage of each of the other impurities in the portion of Cefprozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of cefprozil from the *Standard solution*

C_S = concentration of USP Cefprozil (Z)-isomer RS in the *Standard solution* (mg/mL)

C_U = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of USP Cefprozil (Z)-isomer RS (mg/mg)

Acceptance criteria: See Table 2. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Amoxicillin related compound I ^a	0.40	0.3
Cefadroxil	0.54	0.5
Hydroxyphenyldiketopiperazine ^b	0.61	0.3
Cefprozil related compound D (Z)-isomer ^{c,d}	0.69	0.3
Cefprozil related compound D (E)-isomer ^e	0.91	
O-Acyl cefprozil ^f	0.76	0.2
Cefprozil (Z)-isomer	1.0	—
Cefprozil (E)-isomer	1.37	—
Z-Cefprozil open ring ^g	1.74	0.2
Cefprozil related compound H (Z)-isomer ^{h,i}	1.95	0.2
Cefprozil related compound H (E)-isomer ⁱ	2.19	
E-Cefprozil open ring ^k	2.08	0.2
Cefprozil related compound K ^{l,m}	2.76	0.1
	2.86	0.1
	2.91	0.1
Any individual unspecified impurity	—	0.1
Total impurities	—	2.0

^a (R)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

^b 3-(Aminomethylene)-6-(4-hydroxyphenyl)piperazine-2,5-dione.

^c 7-Amino-3-propenylcephalosporanic acid (Z-isomer); (6R,7R)-7-Amino-8-oxo-3-[(Z)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^d The sum of the two isomers is reported. The limit for the sum is 0.3%.

^e 7-Amino-3-propenylcephalosporanic acid (E-isomer); (6R,7R)-7-Amino-8-oxo-3-[(E)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^f (6R,7R)-7-[(R)-2-Amino-2-{4-[(R)-2-amino-2-(4-hydroxyphenyl)acetoxyl]phenyl}acetamido]-8-oxo-3-[(Z)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^g (R)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl]-5-[(Z)-prop-1-enyl]-3,6-dihydro-2H-1,3-thiazine-4-carboxylic acid.

^h N-Acyl cefprozil (Z-isomer); (6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

ⁱ The sum of the two isomers is reported. The limit for the sum is 0.2%.

^j N-Acyl cefprozil (E-isomer); (6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(E)-prop-1-enyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^k (R)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido](carboxy)methyl]-5-[(E)-prop-1-enyl]-3,6-dihydro-2H-1,3-thiazine-4-carboxylic acid.

^l Hydroxyphenyldiketopiperazine lactone; 3-(5-Ethyl-7-oxo-2,4,5,7-tetrahydro-1H-furo[3,4-d][1,3]thiazin-2-yl)-6-(4-hydroxyphenyl)piperazine-2,5-dione.

^m The system resolves four isomers of cefprozil related compound K.

■1S (USP36)

Add the following:**• ORGANIC IMPURITIES, PROCEDURE 2**

Use *Organic Impurities, Procedure 2* when the impurity profile includes ethoxycarbonyl cefprozil, methoxycefadroxil, cefprozil delta-3 isomer, cefprozil amide, and cefprozil dimer.

Solution A: 4 g/L of monobasic sodium phosphate adjusted with dilute phosphoric acid (1 in 10) to a pH of 4.2 ± 0.05

Solution B: Acetonitrile and *Solution A* (1:1)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	95	5
20	70	30
40	40	60
50	0	100
60	0	100
62	95	5
70	95	5

Diluent: 0.85 g/L of monobasic potassium phosphate and 1.16 g/L of anhydrous dibasic sodium phosphate in water

System suitability stock solution: 0.15 mg/mL of USP Cefadroxil RS and 0.75 mg/mL of USP Cefprozil Related Compound D RS, prepared as follows. Dissolve USP Cefadroxil RS in *Solution A*, using 20% of the final volume. Add USP Cefprozil Related Compound D RS, mix, and dilute with *Diluent* to volume.

System suitability solution: 15 µg/mL of USP Cefadroxil RS and 75 µg/mL of USP Cefprozil Related Compound D RS from the *System suitability stock solution* and 1.5 mg/mL of USP Cefprozil RS in *Solution A*

Standard solution: 15 µg/mL of USP Cefprozil RS in *Solution A*

Sample solution: 1.5 mg/mL of Cefprozil in *Solution A*. Refrigerate the solution, and use within 1 h.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: NMT 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Autosampler temperature: 4°

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between the (Z)-isomer of cefprozil related compound D and cefadroxil; NLT 1.5 between cefadroxil and the (E)-isomer of cefprozil related compound D, *System suitability solution*

Relative standard deviation: NMT 5.0% for the sum of the cefprozil (Z)-isomer and cefprozil (E)-isomer, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Cefprozil taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times P \times 1/F \times 100$$

r_u = peak response of each impurity from the *Sample solution*

r_s = sum of the responses for cefprozil (Z)-isomer and cefprozil (E)-isomer from the *Standard solution*

C_s = concentration of USP Cefprozil RS in the *Standard solution* (mg/mL)

C_u = concentration of Cefprozil in the *Sample solution* (mg/mL)

P = potency of USP Cefprozil RS (mg/mg)

F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*. The reporting threshold is 0.05%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amoxicillin related compound I ^a	0.17	1.5	0.15
Cefprozil related compound D (Z)-isomer ^b	0.57	0.56	0.2
Cefadroxil	0.62	1.1	1.0
Methoxycefadroxil ^c	0.65	0.44	0.15
Cefprozil related compound D (E)-isomer ^d	0.73	0.56	0.2
Cefprozil delta-3 isomer ^e	0.92	0.95	0.2
Cefprozil (Z)-isomer	1.0	—	—
Cefprozil (E)-isomer	1.17	—	—
Cefprozil related compound H ^f	1.33	0.93	0.15
Cefprozil amide ^g	1.46	0.90	0.15
Ethoxycarbonylcefprozil ^h	2.08	0.70	0.15
Cefprozil dimer	2.21	0.90	0.2
Any individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	1.5

^a (R)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

^b 7-Amino-3-propenylcephalosporanic acid (Z-isomer); (6R,7R)-7-Amino-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^c (6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^d 7-Amino-3-propenylcephalosporanic acid (E-isomer); (6R,7R)-7-Amino-8-oxo-3-[(E)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^e (6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid.

^f N-Acyl cefprozil (Z-isomer); (6R,7R)-7-[(R)-2-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

^g (R)-2-[(6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxamido]-2-(4-hydroxyphenyl)acetic acid.

^h (6R,7R)-7-[(R)-2-Amino-2-[4-(ethoxycarbonyloxy)phenyl]acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

ⁱ (6R,7R)-7-[(R)-2-[(6R,7R)-7-[(R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxamido]-2-(4-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-prop-1-en-1-yl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

■1S (USP36)

SPECIFIC TESTS

• **CRYSTALLINITY** ⟨695⟩: Meets the requirements

• **PH** ⟨791⟩

Sample solution: 5 mg/mL in water

Acceptance criteria: 3.5–6.5

• **WATER DETERMINATION, Method I** ⟨921⟩: 3.5%–6.5%

• **CEFPROZIL (E)-ISOMER RATIO**

Buffer, Mobile phase, Standard solution 1, Standard solution 2, System suitability solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Calculate the ratio of the cefprozil (*E*)-isomer to total cefprozil in the portion of Cefprozil taken:

$$\text{Result} = E/(E + Z)$$

E = amount of cefprozil (*E*)-isomer as determined in the *Assay* (μg/mg)

Z = amount of cefprozil (*Z*)-isomer as determined in the *Assay* (μg/mg)

Acceptance criteria: The ratio is 0.06–0.11.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** If a test for *Organic Impurities* other than *Procedure 1* is used, then the labeling states with which *Organic Impurities* test the article complies.

Change to read:• **USP REFERENCE STANDARDS** <11>

■ USP Amoxicillin Related Compound I RS

(*R*)-2-Amino-2-(4-hydroxyphenyl)acetic acid.

$\text{C}_8\text{H}_9\text{NO}_3$ 167.16_{1S} (USP36)

USP Cefadroxil RS

■ USP Cefprozil RS_{1S} (USP36)

USP Cefprozil (*E*)-Isomer RS

USP Cefprozil (*Z*)-Isomer RS

■ USP Cefprozil Related Compound D RS

7-Amino-3-propenylcephalosporanic acid; (6*R*,7*R*)-

7-Amino-8-oxo-3-[(*Z*)-prop-1-enyl]-5-thia-1-azabicyclo

[4.2.0]oct-2-ene-2-carboxylic acid.

$\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ 240.28_{1S} (USP36)

Cetirizine Hydrochloride Tablets**DEFINITION**

Cetirizine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of cetirizine hydrochloride ($\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}_3 \cdot 2\text{HCl}$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY• **PROCEDURE**

Solution A: 2 N sulfuric acid and water (2:33)

Buffer: 2.9 mL/L of phosphoric acid in water

Mobile phase: Acetonitrile and *Buffer* (3:7)

Diluent: Acetonitrile, *Solution A*, and water (100:1:100)

Standard solution: 0.2 mg/mL of USP Cetirizine Hydrochloride RS in *Diluent*

Sample solution: 0.2 mg/mL of cetirizine hydrochloride in *Diluent* from NLT 20 powdered Tablets. [NOTE—Sonicate, if necessary.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 μL

Run time: 1.3 times the retention time of cetirizine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of cetirizine hydrochloride ($\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}_3 \cdot 2\text{HCl}$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Cetirizine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of cetirizine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS**Change to read:**• **DISSOLUTION** <711>

• **Test 1** (RB 1-Aug-2012)

Medium: Water; 900 mL, degassed

Apparatus 2: 50 rpm

Time: 30 min

Buffer: 2.9 mL/L of phosphoric acid in water

Mobile phase: Acetonitrile and *Buffer* (2:3)

Standard solution: 11 μg/mL of USP Cetirizine Hydrochloride RS in water. This solution can be stored for 48 h at room temperature.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Flow rate: 1 mL/min

Injection volume: 50 μL

Run time: 1.3 times the retention time of cetirizine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of cetirizine hydrochloride ($\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}_3 \cdot 2\text{HCl}$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the • *Sample solution* • (RB

1-Aug-2012)

r_S = peak response from the • *Standard solution* • (RB

1-Aug-2012)

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of cetirizine hydrochloride ($\text{C}_{21}\text{H}_{25}\text{ClN}_2\text{O}_3 \cdot 2\text{HCl}$) is dissolved.

• **Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Water; 900 mL

Apparatus 2: 75 rpm

Time: 30 min

Buffer: 0.4 g/L of 1-heptane sulfonic acid sodium salt

Mobile phase: Acetonitrile and *Buffer* (50:50). Adjust with 0.1 N sulfuric acid to a pH of 3.5.

Standard solution: 11 µg/mL of USP Cetirizine Hydrochloride RS in *Medium*

Sample solution: Pass a 20-mL portion of the solution under test through a nylon filter of 0.45-µm pore size. Discard the first 10 mL of filtrate.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: 1.6 times the retention time of cetirizine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Cetirizine Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) is dissolved.

• **Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: ($L/900$) mg/mL of USP Cetirizine Hydrochloride RS in water, where L is the label claim of cetirizine hydrochloride, in mg/Tablet

Sample solution: Centrifuge a portion of the solution under test for NLT 15 min at 3000 rpm.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV

Analytical wavelength: UV 231 nm

Blank: *Medium*

Path length: 1 cm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Cetirizine Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of cetirizine hydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) is dissolved. • (RB 1-Aug-2012)

• **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

IMPURITIES

Change to read:

• ORGANIC IMPURITIES

Solution A: 2 N sulfuric acid and water (2:33)

Buffer: 3.4 g/L of tetrabutyl ammonium hydrogen sulfate in water

Diluent: Acetonitrile, *Solution A*, and water (910:27:63)

Mobile phase: Acetonitrile, *Solution A*, and *Buffer* (93:5:2)

Standard solution: 1.5 µg/mL of USP Cetirizine Hydrochloride RS in *Diluent*

Sample solution: 0.5 mg/mL of cetirizine hydrochloride in *Diluent* from NLT 20 powdered Tablets. [NOTE—Sonicate, if necessary.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.0-mm × 25-cm; 5-µm packing L3

Flow rate: 0.8 mL/min

Injection volume: 20 µL

Run time: 2.5 times the retention time of cetirizine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 10.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of cetirizine from the *Standard solution*

C_S = concentration of USP Cetirizine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of cetirizine hydrochloride in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Cetirizine lactose ester ^a	0.56	1.0	0.40
Cetirizine	1.0	—	—
Cetirizine ethanol ^b	1.67	1.2	0.2 • (RB 1-Aug-2012)
Any unspecified degradation product	—	—	0.2
Total impurities	—	—	0.8

^a 6-O-[2-(2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetyl]-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose.

^b 2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethanol.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store below 30°.

Add the following:

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. • (RB 1-Aug-2012)
- **USP REFERENCE STANDARDS** <11>
USP Cetirizine Hydrochloride RS

Add the following:**Ciprofloxacin Extended-Release Tablets****DEFINITION**

Ciprofloxacin Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY• **PROCEDURE**

Buffer: Dilute 2.9 mL of phosphoric acid in water to 1000 mL. Adjust with triethylamine to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (135:865)

System suitability solution: 0.58 mg/mL of USP Ciprofloxacin Hydrochloride RS and 0.5 mg/mL of USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase*

Standard stock solution: 1.16 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase*

Standard solution: 0.058 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* from *Standard stock solution*

Sample stock solution: Nominally 0.5 mg/mL in *Mobile phase* prepared as follows. Transfer an equivalent to 250 mg of ciprofloxacin from finely powdered Tablets (NLT 20) to a 500-mL volumetric flask, add 400 mL of *Mobile phase*, place on a rotary shaker for 15 min, and sonicate for 25 min. Allow the solution to cool to room temperature, and dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter of 0.45- μ m pore size.

Sample solution: Nominally 0.05 mg/mL of ciprofloxacin in water from *Sample stock solution*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 278 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 6 between the ciprofloxacin and ciprofloxacin ethylenediamine analog peaks, *System suitability solution*

Tailing factor: NMT 4.0 for the ciprofloxacin peak, *System suitability solution*

Relative standard deviation: NMT 2.0% for the ciprofloxacin peak, *Standard solution*

Analysis

Samples: *Sample solution* and *Standard solution*
Calculate the percentage of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of ciprofloxacin from the *Sample solution*

r_S = peak response of ciprofloxacin from the *Standard solution*

C_S = concentration of USP Ciprofloxacin Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ciprofloxacin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of ciprofloxacin hydrochloride, 367.81

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS• **DISSOLUTION** <711>

Medium: pH 4.5 acetate buffer (transfer 3 g of sodium acetate and 14 mL of 2 N acetic acid to a 1-L volumetric flask, and dilute with water to volume); 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 30, 60, and 120 min

Standard solution: 6.5 μ g/mL of USP Ciprofloxacin Hydrochloride RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45- μ m pore size. For 500-mg Tablets: transfer 2 mL of the filtrate to a 200-mL volumetric flask, and dilute with *Medium* to volume. For 1000-mg Tablets: transfer 1 mL of the filtrate to a 200-mL volumetric flask, and dilute with *Medium* to volume. Replace the aliquots withdrawn for analysis with fresh portions of *Medium*.

Analysis

Mode: UV

Analytical wavelength: 277 nm

Blank: *Medium*

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at each time interval (D_i):

$$D_i = (A_U/A_S) \times (C_S/L) \times (M_{r1}/M_{r2}) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of ciprofloxacin in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of ciprofloxacin hydrochloride, 367.81

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

Percentage of ciprofloxacin dissolved at the first time interval = D_1

Percentage of ciprofloxacin dissolved at the second time interval = $D_2 + [D_1 \times (v/V)]$

Percentage of ciprofloxacin dissolved at the third time interval = $D_3 + [(D_2 + D_1) \times v/V]$

v = volume of solution under test removed at each time interval (mL)

Tolerances

For Tablets labeled to contain 500 mg, see *Table 1*.

Table 1

Time (min)	Amount Dissolved
30	42%–62%
60	62%–87%
120	NLT 80%

For Tablets labeled to contain 1000 mg, see Table 2.

Table 2

Time (min)	Amount Dissolved
30	30%–50%
60	50%–70%
120	NLT 80%

The percentages of the labeled amount of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) dissolved at the times specified conform to Acceptance Table 2 in *Dissolution* (711).

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

• ORGANIC IMPURITIES

Buffer, Mobile phase, and System suitability solution: Proceed as directed in the Assay.

Standard stock solution: 0.5 mg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase*

Standard solution: 1.25 µg/mL of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* from *Standard stock solution*

Sample solution: Nominally 0.5 mg/mL of ciprofloxacin in *Mobile phase* prepared as follows. Transfer an equivalent to 250 mg of ciprofloxacin from finely powdered Tablets (NLT 20) to a 500-mL volumetric flask, add 400 mL of *Mobile phase*, place on a rotary shaker for 15 min, and sonicate for 25 min with intermittent shaking. Allow the solution to cool to room temperature, and dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 263 nm and 278 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection size: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 6 between the ciprofloxacin and ciprofloxacin ethylenediamine analog peaks at 278 nm, *System suitability solution*

Tailing factor: NMT 2.0 for the ciprofloxacin peak at 278 nm, *Standard solution*

Relative standard deviation: NMT 10.0% for the ciprofloxacin peak at 278 nm, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of decarboxyciprofloxacin in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of decarboxyciprofloxacin at 263 nm from the *Sample solution*

r_S = peak responses of ciprofloxacin at 263 nm from the *Standard solution*

C_S = concentration of USP Ciprofloxacin Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ciprofloxacin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of ciprofloxacin hydrochloride, 367.81

F = relative response factor of decarboxyciprofloxacin as shown in Table 3

Calculate the percentage of the other impurities in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity at 278 nm from the *Sample solution*

r_S = peak response of ciprofloxacin at 278 nm from the *Standard solution*

C_S = concentration of USP Ciprofloxacin Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ciprofloxacin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of ciprofloxacin, 331.34

M_{r2} = molecular weight of ciprofloxacin hydrochloride, 367.81

F = relative response factor as shown in Table 3

Acceptance criteria: See Table 3.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Decarboxyciprofloxacin ^a	0.36	1.6	0.2
Desfluorociprofloxacin ^b	0.59	1.0	0.2
Ciprofloxacin ethylenediamine analog ^c	0.68	1.2	0.2
Ciprofloxacin	1.00	—	—
7-Chloro-6-piperazinyl analog ^d	1.20	0.45	0.2
Chlorociprofloxacin ^e	2.10	0.75	0.2
Any unspecified impurity	—	1.0	0.2
Total impurities	—	—	0.6

^a 1-Cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one.

^b 1-Cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

^c 7-(2-Aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

^d 7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

^e 6-Chloro-1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.

• USP REFERENCE STANDARDS (11)

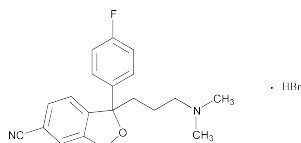
USP Ciprofloxacin Ethylenediamine Analog RS

7-(2-Aminoethylamino)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

$C_{15}H_{16}FN_3O_3$ 305.30

USP Ciprofloxacin Hydrochloride RS₁₅ (USP36)

Citalopram Hydrobromide



$C_{20}H_{21}FN_2O \cdot HBr$ 405.30
 5-Isobenzofurancarboxitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, monohydrobromide;
 1-[3-(Dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalan-carboxitrile monohydrobromide [59729-32-7].

DEFINITION

Citalopram Hydrobromide contains NLT 98.0% and NMT 102.0% of citalopram hydrobromide ($C_{20}H_{21}FN_2O \cdot HBr$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL, Bromide** (191)
Sample solution: 10 mg/mL of Citalopram Hydrobromide in water
Acceptance criteria: Meets the requirement of the silver nitrate precipitate test

ASSAY

Change to read:

• PROCEDURE

Buffer: Dissolve 1 g of sodium acetate in 800 mL of water, and add 6 mL of triethylamine. Adjust with acetic acid to a pH of 4.6, and dilute with water to 1 L.

Mobile phase: Acetonitrile and *Buffer* (20:80). The apparent pH is 5.0 ± 0.1 . Make adjustments, if necessary.

Diluent: Methanol and water (50:50)

Standard solution: 0.625 mg/mL of USP Citalopram Hydrobromide RS in *Diluent*

Sample solution: 0.625 mg/mL of Citalopram Hydrobromide in *Diluent*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 239 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing L7

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 μ L

Run time: 1.3 times the retention time of citalopram. (RB 1-Jan-2013)

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 3000 theoretical plates

Tailing factor: NMT 3.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Diluent*, *Standard solution*, and *Sample solution*

Verify that there are no interfering peaks, using the *Diluent*. Calculate the percentage of citalopram hydrobromide ($C_{20}H_{21}FN_2O \cdot HBr$) in the portion of Citalopram Hydrobromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
 r_S = peak response from the *Standard solution*
 C_S = concentration of USP Citalopram Hydrobromide RS in the *Standard solution* (mg/mL)
 C_U = concentration Citalopram Hydrobromide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

• RESIDUE ON IGNITION (281)

Analysis: Moisten the sample with 2 mL of nitric acid and 5 drops of sulfuric acid.

Acceptance criteria: NMT 0.1%

• HEAVY METALS, Method II (231): NMT 20 ppm

Change to read:

• ORGANIC IMPURITIES, PROCEDURE 1

[NOTE—On the basis of the synthetic route used, perform either *Procedure 1* or *Procedure 2*. However, if the chloro and bromo analogs are potential related compounds in the synthetic route used, *Procedure 2* is recommended.]

Buffer, Mobile phase, Diluent, and Sample solution:

Proceed as directed in the *Assay*.

System suitability solution: 1 μ g/mL each of USP Citalopram Hydrobromide RS and USP Citalopram Related Compound D RS in *Diluent*

Standard solution: 0.625 μ g/mL of USP Citalopram Hydrobromide RS in *Diluent*

Sensitivity solution: 0.0625 μ g/mL of USP Citalopram Hydrobromide RS in *Diluent*

Chromatographic system: Proceed as directed in the *Assay* except use a *Run time* of 1.7 times the retention time of citalopram. (RB 1-Jan-2013)

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.8 between citalopram related compound D and citalopram, *System suitability solution*

Tailing factor: 0.8–1.5 for citalopram, *System suitability solution*

Relative standard deviation: NMT 5% for citalopram, *System suitability solution*

Signal-to-noise ratio: NLT 3, *Sensitivity solution*

Analysis

Samples: *Diluent*, *Standard solution*, and *Sample solution*

Verify that there are no interfering peaks, using the *Diluent*. Calculate the percentage of each impurity in the portion of Citalopram Hydrobromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of citalopram from the *Standard solution*

C_S = concentration of USP Citalopram Hydrobromide RS in the *Standard solution* (mg/mL)

C_U = concentration of Citalopram Hydrobromide in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of citalopram, 324.39

M_{r2} = molecular weight of citalopram hydrobromide, 405.30

F = relative response factor (see *Table 1*)

Acceptance criteria: See Table 1.

Table 1

Name	Relative Retention Time	Relative Response Factor ^a (RB 1-Jan-2013)	Acceptance Criteria, NMT (%)
Citalopram ketone ^b (RB 1-Jan-2013)	0.13	0.34	0.1
Citalopram related compound A	0.18	0.77	0.1
Citalopram open ring ^c (RB 1-Jan-2013)	0.26	0.99	0.1
Citalopram related compound B ^d (RB 1-Jan-2013)	0.40	0.98	0.1
Citalopram related compound C	0.67	0.69	0.1
Citalopram related compound D	0.90	1.04	0.1
Citalopram	1.0	—	—
Citalopram related compound E ^e (RB 1-Jan-2013)	1.29	0.91	0.1
Individual unknown impurity	—	1.0	0.1
Total impurities	—	—	0.5

^a The relative response factors provided are for each impurity relative to citalopram (free base).

^b 4-(Dimethylamino)-1-[1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-yl]butan-1-one.

^c 4-[4-(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile.

^d 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile.

^e 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile-*N*-oxide. (RB 1-Jan-2013)

Change to read:

ORGANIC IMPURITIES, PROCEDURE 2

Buffer: To each L of 2.7 g/L of monobasic potassium phosphate in water prepared, add 1 mL of *N,N*-dimethyloctylamine, and adjust with phosphoric acid to a pH of 3.0.

Solution A: Methanol, tetrahydrofuran, and Buffer (24:6:70)

Solution B: Acetonitrile and Buffer (80:20)

Mobile phase: See Table 2.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
18	100	0
40	10	90
45	10	90
46	100	0
55	100	0

Diluent: Acetonitrile and Buffer (30:70)

System suitability solution: 1.5 µg/mL each of USP Citalopram Hydrobromide RS, USP Citalopram Related Compound A RS, USP Citalopram Related Compound C RS, USP Citalopram Related Compound D RS, USP Citalopram Related Compound G RS, and USP Citalopram Related Compound H RS in Diluent

Standard solution: 1.5 µg/mL of USP Citalopram

Hydrobromide RS in Diluent. (RB 1-Jan-2013)

Sample solution: 1.5 mg/mL of Citalopram

Hydrobromide in Diluent

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 224 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 0.8 mL/min

Injection volume: 10 µL

System suitability

Sample: System suitability solution. (RB 1-Jan-2013)

[NOTE—See Table 3 for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between citalopram and citalopram related compound D; NLT 4.0 between citalopram related compound G and citalopram related compound H

Relative standard deviation: NMT 2.0% for citalopram

Analysis

Samples: System suitability solution, Standard solution, and Sample solution

Chromatograph the System suitability solution, and identify the components on the basis of their relative retention times, as shown in Table 3. Calculate the percentage of each impurity in the portion of Citalopram Hydrobromide taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

r_u = peak area of each impurity from the Sample solution

r_s = peak area of citalopram from the Standard solution

C_s = concentration of USP Citalopram Hydrobromide RS in the Standard solution (mg/mL)

C_u = concentration of Citalopram Hydrobromide in the Sample solution (mg/mL)

F = relative response factor (see Table 3). (RB 1-Jan-2013)

Acceptance criteria: See Table 3.

Table 3

Name	Relative Retention Time	Relative Response Factor ^a	Acceptance Criteria, NMT (%)
Bromide ^b	0.24	—	—
Citalopram related compound A	0.40	0.73	0.15
Citalopram related compound C	0.88	1.7	0.15
Citalopram	1.0	—	—
Citalopram related compound D	1.09	0.93	0.15
Citalopram related compound G	2.20	1.2	0.15
Citalopram related compound H	2.30	1.1	0.15
Individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.75

^a The relative response factors provided are for each impurity relative to citalopram hydrobromide.

^b This peak is due to the counterion. It is not an impurity and should not be included in the Total impurities.

(RB 1-Jan-2013)

SPECIFIC TESTS

- **OPTICAL ROTATION**, *Specific Rotation* (781S)
Sample solution: 25 mg/mL of Citalopram Hydrobromide in methanol
Acceptance criteria: -0.2° to $+0.2^{\circ}$ at 20°
- **PH** (791)
Sample solution: 5 mg/mL of Citalopram Hydrobromide in water
Acceptance criteria: 5–6.5
- **WATER DETERMINATION**, *Method I* (921)
Sample: 250 mg of Citalopram Hydrobromide
Acceptance criteria: NMT 0.5%
- **COMPLETENESS OF SOLUTION**
Blank: 96% alcohol
Sample solution: 25 mg/mL of Citalopram Hydrobromide in 96% alcohol
Analytical wavelength: 410 nm
Acceptance criteria: Absorbance is NMT 0.040 in a 1-cm quartz cell

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **LABELING:** If a procedure for *Organic Impurities* other than *Procedure 1* is used, then the labeling states with which *Organic Impurities* procedure the article complies.

Change to read:

- **USP REFERENCE STANDARDS** (11)
 USP Citalopram Hydrobromide RS
 • USP Citalopram Related Compound A RS
 1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide.
 $C_{20}H_{23}FN_2O_2$ 342.41
 USP Citalopram Related Compound C RS
 3-(3-Dimethylaminopropyl)-3-(4-fluorophenyl)-6-cyano-1(3H)-isobenzofuranone oxalate.
 $C_{20}H_{19}FN_2O_2 \cdot C_2H_2O_4$ 428.42
 USP Citalopram Related Compound D RS
 [NOTE—May be available as a hydrochloride or a hydrobromide salt.]
 1-(4-Fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrochloride.
 $C_{19}H_{19}FN_2O \cdot HCl$ 346.83
 1-(4-Fluorophenyl)-1-(3-methylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide.
 $C_{19}H_{19}FN_2O \cdot HBr$ 391.28
 USP Citalopram Related Compound G RS
 3-[5-Chloro-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-N,N-dimethylpropan-1-amine hydrobromide.
 $C_{19}H_{21}ClFNO \cdot HBr$ 414.74
 USP Citalopram Related Compound H RS
 3-[5-Bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl]-N,N-dimethylpropan-1-amine hydrobromide.
 $C_{19}H_{21}BrFNO \cdot HBr$ 459.19● (RB 1-Jan-2013)

Clotrimazole Vaginal Inserts**DEFINITION**

Clotrimazole Vaginal Inserts contain NLT 90.0% and NMT 110.0% of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$).

IDENTIFICATION**Change to read:**

- **A.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.■1S (USP36)

ASSAY**PROCEDURE**

Buffer: 4.35 g/L of dibasic potassium phosphate

Mobile phase: Methanol and *Buffer* (3:1). Pass through a filter of 0.2- μ m or finer pore size. The ratio of volumes may be changed to obtain the required resolution.

Internal standard solution: Transfer 66 mg of testosterone propionate to a 100-mL volumetric flask, dissolve in 75 mL of methanol, and dilute with *Buffer* to volume.

Standard solution: 1 mg/mL of USP Clotrimazole RS prepared as follows. Transfer 50 mg of USP Clotrimazole RS to a 50-mL volumetric flask, add 5.0 mL of the *Internal standard solution*, and dilute with *Mobile phase* to volume.

System suitability stock solution: 0.2 mg/mL of USP Clotrimazole Related Compound A RS in methanol

System suitability solution: Transfer 12.0 mL of the *System suitability stock solution* to a 25-mL volumetric flask, add 4 mL of *Buffer* and 3 mL of the *Standard solution*, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 1 mg/mL of clotrimazole prepared as follows. Transfer an equivalent to 100 mg of clotrimazole from finely powdered Vaginal Inserts (NLT 10) to a 50-mL screw-capped centrifuge tube. Add 10.0 mL of the *Internal standard solution* and 15 mL of *Mobile phase*, rotate for 15 min, and centrifuge for 10 min. Using a suitable syringe, transfer the supernatant to a 100-mL volumetric flask. Rinse the syringe with 25 mL of *Mobile phase*, adding the rinsings to the centrifuge tube. Rotate the centrifuge tube for 15 min, and centrifuge for 10 min. Using a suitable syringe, transfer the supernatant to the 100-mL volumetric flask. Rinse the syringe with 25 mL of *Mobile phase*, and add the washings to the volumetric flask. Dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Columns

Guard: 2.1-mm \times 6-cm; 10- μ m packing L7

Analytical: 3.9-mm \times 30-cm; 10- μ m packing L1

Flow rate: 1 mL/min

Injection volume: 20 μ L

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for clotrimazole related compound A, clotrimazole, and testosterone propionate are about 0.9, 1.0, and 1.5, respectively.]

Suitability requirements

Resolution: NLT 1.2 between clotrimazole related compound A and clotrimazole, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) in the portion of Vaginal Inserts taken:

$$\text{Result} = (R_u/R_s) \times (C_s/C_u) \times 100$$

- R_U = peak response ratio of clotrimazole to testosterone propionate from the *Sample solution*
 R_S = peak response ratio of clotrimazole to testosterone propionate from the *Standard solution*
 C_S = concentration of USP Clotrimazole RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of clotrimazole in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISINTEGRATION** (701)
Time: 20 min
Acceptance criteria: Meet the requirements
- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **USP REFERENCE STANDARDS** (11)
USP Clotrimazole RS
USP Clotrimazole Related Compound A RS
(*o*-Chlorophenyl)diphenylmethanol.
 $C_{19}H_{15}ClO$ 294.78

Clotrimazole Lozenges**DEFINITION**

Clotrimazole Lozenges contain NLT 90.0% and NMT 110.0% of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) in a suitable molded base.

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, both relative to the internal standard, as obtained in the Assay.

Delete the following:

- **B. THIN-LAYER CHROMATOGRAPHY**

Solution A: Dissolve 3 g of bismuth subnitrate and 30 g of potassium iodide in 10 mL of dilute hydrochloric acid (1 in 4), and dilute with water to 100 mL.

Standard solution: 2.5 mg/mL of USP Clotrimazole RS in dichloromethane

Sample solution: Place an equivalent to 50 mg of clotrimazole, from a quantity of finely powdered Lozenges, into a screw-capped 50-mL test tube, and add 20.0 mL of dichloromethane. Shake by mechanical means for 10 min, and allow the suspension to settle. Use the supernatant.

Chromatographic system

(See *Chromatography* (621), *Thin-Layer Chromatography*.)

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 20 μ L

Developing solvent system: Diethyl ether and ammonium hydroxide (8:1)

Spray reagent: Dilute 10 mL of *Solution A* and 10 mL of dilute hydrochloric acid (1 in 4) with water to 100 mL.

Analysis

Samples: *Standard solution* and *Sample solution*
Position the plate in a chromatographic chamber, and develop the chromatograms in the *Developing solvent*

system until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, and then spray with the *Spray reagent*.

Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*, and after the plates have been sprayed with the *Spray reagent*, the clotrimazole spots are orange. ■1S (USP36)

ASSAY

- **PROCEDURE**

Buffer: 1 g/L of ammonium carbonate in water. Adjust with 10% sulfuric acid solution to a pH of 6.0.

Mobile phase: Methanol and *Buffer* (75:25)

Internal standard stock solution: 5 mg/mL of triphenylmethane in methanol

Internal standard solution: 0.2 mg/mL of triphenylmethane in *Mobile phase* from *Internal standard stock solution*

Standard solution: 0.2 mg/mL of USP Clotrimazole RS prepared as follows. Transfer about 20 mg of USP Clotrimazole RS to a 100-mL volumetric flask. Add 4.0 mL of *Internal standard stock solution*, and dissolve in and dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.1 mg/mL of clotrimazole prepared as follows. Transfer an equivalent to 5 mg of clotrimazole, from weighed and pulverized Lozenges (NLT 10), to a 50-mL screw-capped centrifuge tube. Pipet 25 mL of *Internal standard solution* into the tube. Sonicate for 10 min, then shake for 10 min. Centrifuge at 2500 rpm for 30 min. Use the clear supernatant layer.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 3.9-mm \times 30-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 20 μ L

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for clotrimazole and triphenylmethane are about 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 1.5 between clotrimazole and triphenylmethane

Column efficiency: NLT 1500 theoretical plates

Tailing factor: NMT 2

Relative standard deviation: NMT 2.0% for replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) in the portion of Lozenges taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of clotrimazole to triphenylmethane from the *Sample solution*

R_S = peak response ratio of clotrimazole to triphenylmethane from the *Standard solution*

C_S = concentration of USP Clotrimazole RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of clotrimazole in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• DISSOLUTION (711)

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated

Apparatus 2: 50 rpm

Time: 45 min

Determine the amount of clotrimazole ($C_{22}H_{17}ClN_2$) dissolved by using the following method.

Buffer A: 4.4 mg/mL of dibasic potassium phosphate in water

Buffer B: 17.4 mg/mL of dibasic potassium phosphate in water

Diluent: Methanol and *Buffer B* (60:40)

Mobile phase: Methanol and *Buffer A* (4:1)

Standard stock solution: 0.02 mg/mL of USP Clotrimazole RS in *Medium*

Standard solution: 4 µg/mL from the *Standard stock solution* in *Diluent*

Sample solution: Withdraw 25 mL of the solution under test from the vessel. Pass through a polyvinylidene difluoride filter of 0.45-µm pore size, and discard the first 10 mL of the filtrate. Transfer 5.0 mL of filtrate to a 25-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 3.9-mm × 7.5-cm; packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times D \times V \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim of clotrimazole (mg/Lozenge)

D = dilution factor for the *Sample solution*, 5

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.

- **USP REFERENCE STANDARDS** (11)
USP Clotrimazole RS

Clotrimazole Topical Solution

DEFINITION

Clotrimazole Topical Solution is a solution of Clotrimazole in a suitable nonaqueous, hydrophilic solvent. It contains NLT 90.0% and NMT 115.0% of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$).

IDENTIFICATION

Change to read:

- **A.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, both relative to the internal standard, as obtained in the *Assay*.

■ IS (USP36)

ASSAY

• PROCEDURE

Buffer: 4.35 g/L of dibasic potassium phosphate in water

Mobile phase: Methanol and *Buffer* (3:1). Pass through a filter of 0.2-µm or finer pore size.

Internal standard solution: Transfer 66 mg of testosterone propionate to a 100-mL volumetric flask, dissolve in 75 mL of methanol, and dilute with *Buffer* to volume.

Standard solution: 1 mg/mL of USP Clotrimazole RS prepared as follows. Transfer 50 mg of USP Clotrimazole RS to a 50-mL volumetric flask, add 5.0 mL of the *Internal standard solution*, and dilute with *Mobile phase* to volume.

System suitability stock solution: 0.2 mg/mL of USP Clotrimazole Related Compound A RS in methanol

System suitability solution: Add 12.0 mL of the *System suitability stock solution* to a 25-mL volumetric flask. Add 4 mL of *Buffer*, 3 mL of the *Standard solution*, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 1 mg/mL of clotrimazole prepared as follows. Transfer a volume of Topical Solution, equivalent to 50 mg of clotrimazole, to a 50-mL volumetric flask. Add 5.0 mL of the *Internal standard solution*, and dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Columns

Guard: 2.1-mm × 6-cm; 10-µm packing L7

Analytical: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for clotrimazole related compound A, clotrimazole, and testosterone propionate are 0.9, 1.0, and 1.5, respectively.]

Suitability requirements

Resolution: NLT 1.2 between clotrimazole related compound A and clotrimazole, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clotrimazole ($C_{22}H_{17}ClN_2$) in the portion of Topical Solution taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of clotrimazole to testosterone propionate from the *Sample solution*

R_S = peak response ratio of clotrimazole to testosterone propionate from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

C_U = nominal concentration of clotrimazole in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–115.0%

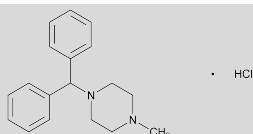
ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers at a temperature between 2° and 30°.
- **USP REFERENCE STANDARDS** (11)
USP Clotrimazole RS
USP Clotrimazole Related Compound A RS
(o-Chlorophenyl)diphenylmethanol.
C₁₉H₁₅ClO 294.78

Cyclizine Hydrochloride

Change to read:

■

■_{1S} (USP36)

C₁₈H₂₂N₂ · HCl 302.84
Piperazine, 1-(diphenylmethyl)-4-methyl-,
monohydrochloride;
1-(Diphenylmethyl)-4-methylpiperazine monohydrochloride
[303-25-3].

DEFINITION

Cyclizine Hydrochloride contains NLT 98.0% and NMT 100.5% of cyclizine hydrochloride (C₁₈H₂₂N₂ · HCl), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)

Delete the following:

- **B.**

Sample: 500 mg

Analysis: Dissolve the *Sample* in 10 mL of a mixture of 3 volumes of alcohol and 2 volumes of water, warming if necessary. Cool the solution in an ice bath, add 1 mL of 1 N sodium hydroxide and 20 mL of water, stir, and filter. Wash the precipitate of the base with water, and dry under vacuum at 60° for 2 h.

Acceptance criteria: It melts between 106° and 109°.

■_{1S} (USP36)

Change to read:

- **■_{1S} (USP36) IDENTIFICATION TESTS—GENERAL, Chloride** (191): Meets the requirements

ASSAY

Change to read:

- **PROCEDURE**

■ [NOTE—In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the endpoint has been reached.] ■_{1S} (USP36)

Sample: ■120 mg ■_{1S} (USP36)

Analysis: ■ Dissolve the *Sample* in 15 mL of anhydrous formic acid. Add 40 mL of acetic anhydride, ■_{1S} (USP36) and

titrate with 0.1 N perchloric acid VS. Perform a blank determination (see *Titrimetry* (541)), and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 15.14 mg of cyclizine hydrochloride (C₁₈H₂₂N₂ · HCl).

Acceptance criteria: 98.0%–100.5% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.2%

Delete the following:

- **PROCEDURE: ORDINARY IMPURITIES** (466)

Standard solution and Sample solution: Methanol

Eluant: Chloroform, methanol, and ammonium hydroxide (80:20:1)

Visualization: 2 ■_{1S} (USP36)

Add the following:

- **ORGANIC IMPURITIES**

[NOTE—Prepare solutions immediately before use.]

Standard solution: 0.05 mg/mL of USP Cyclizine Hydrochloride RS in methanol

Impurity standard solution: 0.25 mg/mL each of USP Cyclizine Hydrochloride RS, USP Cyclizine Related Compound A RS, and USP Benzhydrol RS in methanol

Sample solution: Prepare a solution containing 50 mg/mL of Cyclizine Hydrochloride by dissolving a suitable amount first in methanol, using 80% of the final volume, and then diluting with 1 N sodium hydroxide to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.33-mm × 25-m; coated with a 0.5-μm film of phase G27

Temperatures

Injection port: 250°

Detector: 290°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
100	10	240	0
240	15	270	14

Carrier gas: Helium

Flow rate: 1 mL/min

Injection volume: 1 μL

Injection type: Split ratio, 1:25

System suitability

Sample: *Impurity standard solution*

Suitability requirements

Peak-to-valley ratio: NLT 50 between cyclizine related compound A and methanol

Analysis

Samples: *Standard solution, Impurity standard solution, and Sample solution*

Calculate the percentage of cyclizine related compound A and benzhydrol in the portion of Cyclizine Hydrochloride taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response of each related compound from the *Sample solution*

r_s = peak response of the corresponding related compound from the *Impurity standard solution*

C_s = concentration of the corresponding related compound in the *Impurity standard solution* (mg/mL)

C_U = concentration of Cyclizine Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual impurity in the portion of Cyclizine Hydrochloride taken:

$$\text{Result} = (r_U/r_s) \times (C_s/C_U) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_s = peak response of cyclizine from the *Standard solution*

C_s = concentration of USP Cyclizine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Cyclizine Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See Table 2. Disregard any peak below 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
1-Methylpiperazine (cyclizine related compound A)	0.2	0.5
Benzhydrol	0.7	0.5
Cyclizine	1.0	—
Any other individual impurity	—	0.10
Total impurities	—	1.0

■1S (USP36)

SPECIFIC TESTS

• pH (791)

Sample solution: 20 mg/mL in a mixture of alcohol and water (2:3)

Acceptance criteria: 4.5–5.5

• LOSS ON DRYING (731)

Analysis: Dry a sample at 120° for 3 h.

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Change to read:

• USP REFERENCE STANDARDS (11)

USP Cyclizine Hydrochloride RS

■USP Cyclizine Related Compound A RS

1-Methylpiperazine.

$C_5H_{12}N_2$ 100.16

USP Benzhydrol RS

Diphenylmethanol.

$C_{13}H_{12}O$ 184.23■1S (USP36)

Cyclizine Hydrochloride Tablets

DEFINITION

Cyclizine Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of cyclizine hydrochloride ($C_{18}H_{22}N_2 \cdot HCl$).

IDENTIFICATION

Delete the following:

• A.

Sample: Amount of finely powdered Tablets, equivalent to 500 mg of cyclizine hydrochloride.

Analysis: Shake the *Sample* with 25 mL of water for 5 min, and filter the mixture. Cool the filtrate in an ice bath, add a slight excess of 1 N sodium hydroxide, and stir well. Wash the precipitate of the base with water, and dry under vacuum at 60° for 2 h.

Acceptance criteria: It melts between 106° and 109°.

■1S (USP36)

Add the following:

• A. INFRARED ABSORPTION (197K)

Sample: Extract a quantity of powdered Tablets containing 100 mg of cyclizine hydrochloride with 10 mL of ethanol. Filter, evaporate to dryness, and use the dried residue.

Acceptance criteria: Meet the requirements■1S (USP36)

Delete the following:

• B. IDENTIFICATION—ORGANIC NITROGENOUS BASES (181):

Meet the requirements■1S (USP36)

ASSAY

• PROCEDURE

Analysis: Proceed with Tablets as directed in *Salts of Organic Nitrogenous Bases* (501). Dilute the *Standard Preparation* and the *Assay Preparation*, respectively, with an equal volume of dilute sulfuric acid (1 in 100), and determine the absorbance at the wavelength of maximum absorbance at about 264 nm.

Calculate the percentage of the labeled amount of cyclizine hydrochloride ($C_{18}H_{22}N_2 \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Assay Preparation*

A_S = absorbance of the *Standard Preparation*

C_S = concentration of USP Cyclizine Hydrochloride RS in the *Standard Preparation* (mg/mL)

C_U = nominal concentration of cyclizine hydrochloride in the *Assay Preparation* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

• DISSOLUTION, Procedure for a Pooled Sample (711)

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Analysis: Determine the amount of cyclizine hydrochloride ($C_{18}H_{22}N_2 \cdot HCl$) dissolved by proceeding as directed in the *Assay*, making any necessary modifications.

Tolerances: NLT 75% (Q) of the labeled amount of cyclizine hydrochloride ($C_{18}H_{22}N_2 \cdot HCl$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES**Add the following:****• ORGANIC IMPURITIES****Diluent:** Methanol**Standard solution 1:** 0.05 mg/mL of USP Cyclizine Hydrochloride RS in *Diluent***Standard solution 2:** 0.05 mg/mL of USP Cyclizine Related Compound A RS in *Diluent***System suitability solution:** 1 mg/mL of USP Cyclizine Hydrochloride RS and 1 mg/mL of USP Hydroxyzine Hydrochloride RS in *Diluent***Sample solution:** Triturate a quantity of powdered Tablets containing 100 mg of cyclizine hydrochloride with 10 mL of methanol, and filter.**Chromatographic system**(See *Chromatography* <621>, *Thin-Layer Chromatography*.)**Mode:** TLC**Adsorbent:** 0.25-mm layer of chromatographic silica gel mixture**Application volume:** 20 μ L**Developing solvent system:** Mix methylene chloride, methanol, and ammonium hydroxide (90:8:2). Allow the layers to separate, and use the lower layer.**System suitability****Sample:** *System suitability solution***Suitability requirements****Resolution:** The chromatogram shows two clearly visible and separated spots.**Analysis****Samples:** *Standard solution 1*, *Standard solution 2*, and *Sample solution*Proceed as directed in *Chromatography* <621>, *Thin-Layer Chromatography*. Air-dry the plate for several min, expose it to iodine vapor for 20 min, and examine the plate under short-wavelength UV light.**Acceptance criteria****Cyclizine related compound A:** The spot corresponding to cyclizine related compound A in the *Sample solution* is not more intense than the principal spot obtained from *Standard solution 2* (NMT 0.5%).**Any unspecified impurity:** Any other secondary spot in the chromatogram from the *Sample solution* is not more intense than the principal spot obtained from *Standard solution 1* (NMT 0.5%).

■1S (USP36)

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Change to read:**• USP REFERENCE STANDARDS <11>**

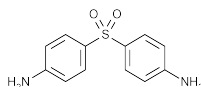
USP Cyclizine Hydrochloride RS

■USP Cyclizine Related Compound A RS

1-Methylpiperazine.

C₅H₁₂N₂ 100.16

USP Hydroxyzine Hydrochloride RS ■1S (USP36)

DapsoneC₁₂H₁₂N₂O₂S
Benzenamine, 4,4'-sulfonylbis-

248.30

4,4'-Sulfonyldianiline [80-08-0].

DEFINITIONDapsone contains NLT 98.0% and NMT 102.0% of dapsone (C₁₂H₁₂N₂O₂S), calculated on the dried basis.**IDENTIFICATION****• A. INFRARED ABSORPTION <197K>****Change to read:**

- B.** ■The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■1S (USP36)

ASSAY**Change to read:****• PROCEDURE****Mobile phase:** Transfer 100 mL of isopropyl alcohol, 100 mL of acetonitrile, and 100 mL of ethyl acetate to a 1000-mL volumetric flask. Add hexane to volume without mixing, then mix, and allow the mixture to cool to room temperature.**Standard solution:** 25 μ g/mL of USP Dapsone RS in *Mobile phase***Sample solution:** 25 μ g/mL of Dapsone in the *Mobile phase***Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 254 nm**Column:** 4-mm \times 30-cm; 10- μ m diameter packing L3

■Flow rate: 1 mL/min ■1S (USP36)

Injection volume: 10 μ L

■Run time: Two times the retention time of Dapsone ■1S (USP36)

System suitability**Sample:** *Standard solution***Suitability requirements****Relative standard deviation:** NMT 2%**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of dapsone (C₁₂H₁₂N₂O₂S) in the portion of Dapsone taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response of the *Sample solution* r_S = peak response of the *Standard solution* C_S = concentration of USP Dapsone RS in the *Standard solution* (μ g/mL) C_U = concentration of Dapsone in the *Sample solution* (μ g/mL)**Acceptance criteria:** 98.0%–102.0% on the dried basis**IMPURITIES****• RESIDUE ON IGNITION <281>:** NMT 0.1%**Change to read:****• SELENIUM <291>**

■Sample: 100-mg sample mixed with 100 mg of magnesium oxide

Acceptance criteria: NMT 30 ppm ■1S (USP36)**Change to read:****• ORGANIC IMPURITIES****Standard solution A:** 12.5 mg/mL of USP Dapsone RS in methanol

■1S (USP36)

Standard solution ■B:■1S (USP36) 62.5 µg/mL of USP Dapsone RS in methanol from *Standard solution A*

Sample solution: 12.5 mg/mL of Dapsone in methanol

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 150- to 200-µm layer of chromatographic silica gel

Application volume: 4 µL

Developing solvent system: Acetone, chloroform, *n*-butyl alcohol, and formic acid (15:60:15:10). Prepare the solvent system fresh daily. Equilibrate the chromatographic chamber with the solvent system for 30 min prior to developing the chromatographic plate.

Spray reagent: 0.1% (w/v) solution of 4-dimethylaminocinnamaldehyde in glacial acetic acid and water (1:1)

Analysis

Samples: *Standard solution* ■A and *Standard solution* ■B:■1S (USP36) and *Sample solution*

Position the plate in a chromatographic chamber, and develop the chromatograms in the developing solvent system until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber and air-dry. Spray the plate lightly with *Spray reagent*. Examine the spots that are developed immediately, and compare the intensities of any secondary spots observed in the *Sample solution* with those of the principal spots of the *Standard solutions*.

Acceptance criteria: No secondary spot from the chromatogram of the *Sample solution* is larger or more intense than the principal spot of *Standard solution* ■B:■1S (USP36) (0.5%), and the sum of the intensities of all the secondary spots of the *Sample solution* corresponds to NMT 1.0%.

SPECIFIC TESTS

Delete the following:

• MELTING RANGE OR TEMPERATURE <741>:

175°–181° ■1S (USP36)

• LOSS ON DRYING <731>

Analysis: Dry at 105° for 3 h.

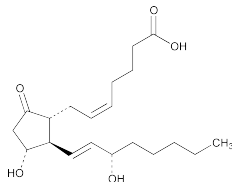
Acceptance criteria: NMT 1.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.

• **USP REFERENCE STANDARDS** <11>
USP Dapsone RS

Dinoprostone



C₂₀H₃₂O₅ 352.47
Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-,
(5Z,11α,13E,15S)-;
(E,Z)-(1R,2R,3R)-7-[3-Hydroxy-2-[(3S)-(3-hydroxy-1-octenyl)]-5-oxocyclopentyl]-5-heptenoic acid;
Prostaglandin E₂ [363-24-6].

DEFINITION

Dinoprostone contains NLT 97.0% and NMT 103.0% of dinoprostone (C₂₀H₃₂O₅).

[NOTE—Prepare all solutions in all tests immediately before use.]

IDENTIFICATION

• A. INFRARED ABSORPTION <197K>

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• PROCEDURE

Mobile phase: Methanol and 0.2% acetic acid (29:21)

Standard solution: 2.5 mg/mL of USP Dinoprostone RS in *Mobile phase*

Sample solution: 2.5 mg/mL of Dinoprostone in *Mobile phase*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 1.0 between dinoprostone and any other adjacent peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dinoprostone (C₂₀H₃₂O₅) in the portion of Dinoprostone taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Dinoprostone RS in the *Standard solution* (mg/mL)

C_U = concentration of Dinoprostone in the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–103.0%

IMPURITIES

• **RESIDUE ON IGNITION** <281>: NMT 0.5%

Change to read:

• ORGANIC IMPURITIES

Mobile phase and Sample solution: Prepare as directed in the *Assay*.

Standard stock solution: Prepare as directed for the *Standard solution* in the *Assay*.

Standard solution: Transfer 0.5 mL of the *Standard stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: ■*Standard solution* ■1S (USP36) and *Sample solution*

Suitability requirements

Resolution: NLT 1.0 between dinoprostone and any other adjacent peak, *Sample solution*

Column efficiency: NLT 6000 theoretical plates,

■ *Standard solution* ■_{1S} (USP36)

Relative standard deviation: ■NMT 10.0%, *Standard solution* ■_{1S} (USP36)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Dinoprostone taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of dinoprostone from the *Standard solution*

C_S = concentration of USP Dinoprostone RS in the *Standard solution* (mg/mL)

C_U = concentration of Dinoprostone in the *Sample solution* (mg/mL)

F = relative response factor (see Table 1)

Acceptance criteria: See Table 1.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
15-Oxo-dinoprostone	0.79	5	—*
15-Epi-dinoprostone	0.85	1.1	—*
8-Isodinoprostone	0.90	1.0	—*
5,6-trans-Dinoprostone	1.15	1.0	2.0
(5Z,13E,15S)-15-Hydroxy-9-oxoprost-5,10,13-triene-1-oic acid	1.80	5	1.0
(5Z,13E,15S)-15-Hydroxy-9-oxoprost-5,8(12),13-trien-1-oic acid	1.90	1.43	1.0
Any individual unspecified impurity	—	1.0	0.10

* The sum of these three impurities is NMT 1.0%.

SPECIFIC TESTS

- **OPTICAL ROTATION, Specific Rotation (781S)**
Sample solution: 5 mg/mL in alcohol
Acceptance criteria: −82.0° to −90.0°, at 20°
- **WATER DETERMINATION, Method I (921):** NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.
- **USP REFERENCE STANDARDS (11)**
 USP Dinoprostone RS

Add the following:

•Diphenhydramine Citrate and Ibuprofen Tablets

DEFINITION

Diphenhydramine Citrate and Ibuprofen Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) and ibuprofen ($C_{13}H_{18}O_2$).

IDENTIFICATION

- **A.** The retention times of the diphenhydramine and ibuprofen peaks from the *Sample solution* correspond to those of the *Standard solution*, as obtained in the Assay.

ASSAY

• PROCEDURE

Buffer A: 6.9 g/L of monobasic sodium phosphate in water

Buffer B: 6.9 g/L of monobasic sodium phosphate in water. Adjust with triethylamine to a pH of 7.2.

Mobile phase: Acetonitrile, triethylamine, glacial acetic acid, and Buffer A (45: 0.2: 0.2: 55)

Diluent: Acetonitrile and Buffer B (3:2)

Standard solution: 1.1 mg/mL of USP Diphenhydramine Citrate RS and 5.7 mg/mL of USP Ibuprofen RS in Diluent. [NOTE—Sonicate as necessary.]

Sample solution: Transfer 10 Tablets into a suitable volumetric flask, add 350 mL of Diluent, and shake with a rotary shaker for 20 min. Sonicate for 20 min with intermediate shaking to obtain a solution containing about 1.1 mg/mL of diphenhydramine citrate and 5.7 mg/mL of ibuprofen. Centrifuge an aliquot at 4000 rpm for 10 min, and use the supernatant. [NOTE—Do not dilute to volume.]

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 5-μm packing L1

Flow rate: 1.2 mL/min

Injection size: 20 μL

Run time: 1.3 times the retention time of ibuprofen

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen

Relative standard deviation: NMT 2.0% for both diphenhydramine and ibuprofen

Analysis

Samples: *Standard solution* and *Sample solution*
 Calculate the percentage of the labeled amounts of diphenhydramine citrate ($C_{17}H_{21}NO \cdot C_6H_8O_7$) and ibuprofen ($C_{13}H_{18}O_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of the corresponding analyte from the *Sample solution*

r_S = peak response of the corresponding analyte from the *Standard solution*

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/mL)

C_U = nominal concentration of the corresponding analyte in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% for both diphenhydramine citrate and ibuprofen

PERFORMANCE TESTS**• DISSOLUTION <711>**

Medium: pH 6.5 phosphate buffer (Transfer 250 mL of 0.2 M monobasic potassium phosphate and 58 mL of 0.2 M sodium hydroxide to a 1000-mL volumetric flask, and dilute with water to volume.); 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 30 min

Buffer solution: 6.9 g/L of sodium dihydrogen phosphate monohydrate in water

Ibuprofen standard stock solution: 1.1 mg/mL of USP Ibuprofen RS in acetonitrile

Diphenhydramine citrate standard stock solution: 1.1 mg/mL of USP Diphenhydramine Citrate RS in water

Standard solution: Transfer 5 mL of the *Ibuprofen standard stock solution* and 1 mL of *Diphenhydramine citrate standard stock solution* to a 25-mL volumetric flask, and dilute with *Medium* to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Mobile phase: Acetonitrile, triethylamine, glacial acetic acid, and *Buffer solution* (45: 0.2: 0.2: 55)

Chromatographic system

(See *Chromatography <621>*, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm, 5-μm packing L1

Flow rate: 1.2 mL/min

Injection size: 20 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen

Relative standard deviation: NMT 2.0% for both diphenhydramine and ibuprofen

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of diphenhydramine and ibuprofen dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response of ibuprofen or diphenhydramine from the *Sample solution*

r_S = peak response of ibuprofen or diphenhydramine from the *Standard solution*

C_S = concentration of ibuprofen or diphenhydramine in the *Standard solution*

L = label claim for ibuprofen or diphenhydramine (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amounts of diphenhydramine and ibuprofen are dissolved.

• UNIFORMITY OF DOSAGE UNITS <905> Meet the requirements**IMPURITIES****• ORGANIC IMPURITIES**

Buffer A: 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 3.2.

Buffer B: 1 mL of phosphoric acid and 1.0 g of monobasic potassium phosphate in 1 L of water. Adjust with triethylamine to a pH of 3.7.

Solution A: Acetonitrile and *Buffer A* (1:4)

Solution B: Acetonitrile and *Buffer B* (1:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	50	50

Table 1 (Continued)

Time (min)	Solution A (%)	Solution B (%)
45	50	50
80	40	60
85	100	0
100	100	0

Standard solution: 0.004 mg/mL of USP Diphenhydramine Citrate RS and 0.02 mg/mL of USP Ibuprofen RS in *Solution B*

System suitability solution: 0.004 mg/mL of USP Diphenhydramine Related Compound A RS, 0.8 mg/mL of USP Diphenhydramine Citrate RS, and 4 mg/mL of USP Ibuprofen RS in *Solution B*

Sample solution: Transfer an amount of powder from ground Tablets (NLT 20) to a suitable volumetric flask. Add 70% of the flask volume of *Solution B*, sonicate for 20 min and dilute with *Solution B* to volume to obtain a solution containing about 0.8 mg/mL of diphenhydramine citrate and 4 mg/mL of ibuprofen. Centrifuge an aliquot at 4000 rpm for 10 min, and use the supernatant.

Chromatographic system

(See *Chromatography <621>*, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-μm packing L1

Flow rate: 1 mL/min

Injection size: 10 μL

System suitability

Samples: *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 0.8 between diphenhydramine and diphenhydramine related compound A, *System suitability solution*

Tailing factor: NMT 2.0 for both diphenhydramine and ibuprofen, *Standard solution*

Relative standard deviation: NMT 5.0% for both diphenhydramine and ibuprofen, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Identify the ibuprofen and diphenhydramine impurities using the relative retention times given in *Table 2*. Calculate the percentage of each diphenhydramine impurity and unspecified impurities in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of diphenhydramine from the *Standard solution*

C_S = concentration of USP Diphenhydramine Citrate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of diphenhydramine citrate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Calculate the percentage of the ibuprofen related impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of the ibuprofen related impurity from the *Sample solution*

r_S = peak response of ibuprofen from the *Standard solution*

C_S = concentration of USP Ibuprofen RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of ibuprofen in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A ^a	0.95	1.3	0.26
Diphenhydramine	1.00	1.0	—
Unidentified diphenhydramine degradation product	1.32	1.0	0.2
Unidentified diphenhydramine degradation product	1.46	1.0	0.2
Unidentified ibuprofen degradation product	1.49	1.0	0.1
Methyl ibuprofen ^{b,c}	1.86	—	—
Unidentified diphenhydramine degradation product	1.96	1.0	0.2
Benzhydryl bromide ^d	2.49	2.4	0.26
Ibuprofen amide ^{b,e}	2.87	—	—
Isopropyl ibuprofen ^{b,f}	3.45	—	—
<i>n</i> -Propyl ibuprofen ^{b,g}	3.71	—	—
<i>meta</i> -Ibuprofen ^{b,h}	5.09	—	—
Ibuprofen	5.31	—	—
<i>n</i> -Butyl ibuprofen ^{b,i}	5.68	—	—
Any other individual unspecified degradation product ^j	—	1.0	0.2
Total impurities ^k	—	—	1.0

^a 2-(Diphenylmethoxy)-*N*-methylethanamine.

^b Process impurity provided for information only; the content is not calculated and not reported.

^c 2-*p*-Tolylpropanoic acid.

^d (Bromomethylene)dibenzene.

^e 2-(4-Isobutylphenyl) propanamide.

^f 2-(4-Isopropylphenyl)propanoic acid.

^g 2-(4-Propylphenyl)propanoic acid.

^h 2-(3-Isobutylphenyl)propanoic acid.

ⁱ 2-(4-Butylphenyl)propanoic acid.

^j Exclude peaks that elute before 4 min or after 80 min.

^k Total impurities excludes ibuprofen related compound C.

• LIMIT OF IBUPROFEN RELATED COMPOUND C

Buffer: 10 g/L of chloroacetic acid in water. Adjust with ammonium hydroxide to a pH of 3.0.

Mobile phase: Acetonitrile and Buffer (3:2)

Internal standard solution: 0.35 mg/mL of valerophenone in Mobile phase

Standard stock solution: 0.6 mg/mL of USP Ibuprofen Related Compound C RS in acetonitrile

Standard solution: 0.012 mg/mL of USP Ibuprofen Related Compound C RS in Internal standard solution; prepared by diluting 2 mL of Standard stock solution with Internal standard solution to 100 mL

Sample solution: Transfer an amount of powder equivalent to 1200 mg of ibuprofen from ground Tablets (NLT 20) to a suitable volumetric flask. Add 100 mL of Internal standard solution, and sonicate for 20 min to obtain a solution containing about 12 mg/mL of ibuprofen. Pass through a suitable filter, and use the filtrate. [NOTE—Do not dilute to volume.]

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Flow rate: 2 mL/min

Injection size: 5 μL

System suitability

Sample: Standard solution

[NOTE—The relative retention times for valerophenone and ibuprofen related compound C are 0.86 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.5 for both valerophenone and ibuprofen related compound C

Relative standard deviation: NMT 2.0%

Resolution: NLT 2.5 between the valerophenone and ibuprofen related compound C peaks

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of ibuprofen related compound C (C₁₂H₁₆O) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak area ratio of ibuprofen to valerophenone from the Sample solution

R_S = peak area ratio of ibuprofen to valerophenone from the Standard solution

C_S = concentration of USP Ibuprofen Related Compound C RS in the Standard solution (mg/mL)

C_U = nominal concentration of ibuprofen in the Sample solution (mg/mL)

Acceptance criteria: NMT 0.1% of ibuprofen related compound C

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS <11>**

USP Diphenhydramine Citrate RS

USP Diphenhydramine Related Compound A RS

2-(Diphenylmethoxy)-*N*-methylethanamine hydrochloride.

C₁₆H₁₉NO · HCl 277.79

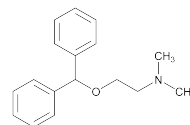
USP Ibuprofen RS

USP Ibuprofen Related Compound C RS

4-Isobutylacetophenone.

C₁₂H₁₆O 176.25 ■₁₅ (USP36)

Diphenhydramine Hydrochloride



C₁₇H₂₁NO · HCl 291.82
 Ethanamine, 2-(diphenylmethoxy)-*N,N*-dimethyl-, hydrochloride;
 2-(Diphenylmethoxy)-*N,N*-dimethylethanamine hydrochloride [147-24-0].

DEFINITION

Diphenhydramine Hydrochloride contains NLT 98.0% and NMT 102.0% of diphenhydramine hydrochloride (C₁₇H₂₁NO · HCl), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** <197K>
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL, Chloride** <191>

ASSAY**Change to read:**• **PROCEDURE**

- **Buffer:** 5.4 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH to 3.0.
- **Diluent:** Acetonitrile and *Buffer* (35:65)
- **System suitability solution:** 0.1 mg/mL each of USP Diphenhydramine Hydrochloride RS and USP Diphenhydramine Related Compound A RS in *Diluent*
- **Standard solution:** 0.07 mg/mL of USP Diphenhydramine Hydrochloride RS in *Diluent*
- **Sample solution:** 0.07 mg/mL of Diphenhydramine Hydrochloride in *Diluent*
- **Mobile phase:** See *Table 1*.

Table 1

Time (min)	Buffer (%)	Acetonitrile (%)
0	65	35
4	65	35
7	20	80
9	65	35
13	65	35

Chromatographic system(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 220 nm**Column:** 4.6-mm × 25-cm; 5-μm packing L7**Flow rate:** 1.2 mL/min**Injection volume:** 10 μL**System suitability****Samples:** *System suitability solution* and *Standard solution***Suitability requirements**

[NOTE—The relative retention times for diphenhydramine related compound A and diphenhydramine are 0.9 and 1.0, respectively.]

Resolution: NLT 1.5 between diphenhydramine related compound A and diphenhydramine, *System suitability solution***Tailing factor:** NMT 1.8, *Standard solution***Relative standard deviation:** NMT 0.85% for six replicate injections, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of diphenhydramine hydrochloride (C₁₇H₂₁NO · HCl) in the portion of sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response from the *Sample solution* r_S = peak response from the *Standard solution* C_S = concentration of USP Diphenhydramine Hydrochloride RS in the *Standard solution* (mg/mL) C_U = concentration of Diphenhydramine Hydrochloride in the *Sample solution* (mg/mL)**Acceptance criteria:** 98.0%–102.0% on the dried basis ¹ (USP36)**IMPURITIES**

- **RESIDUE ON IGNITION** <281>: NMT 0.1%

Add the following:• **ORGANIC IMPURITIES****Buffer:** 5.4 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.0.**Mobile phase:** Acetonitrile and *Buffer* (35:65)**System suitability solution:** 0.1 mg/mL each of USP Diphenhydramine Related Compound A RS, benzhydrol, and USP Diphenhydramine Hydrochloride RS in *Mobile phase***Standard solution:** 0.0035 mg/mL of USP Diphenhydramine Hydrochloride RS in *Mobile phase***Sample solution:** 0.7 mg/mL of Diphenhydramine Hydrochloride in *Mobile phase***Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 220 nm**Column:** 4.6-mm × 25-cm; 5-μm packing L7**Flow rate:** 1.2 mL/min**Injection volume:** 10 μL**Run time:** 7 times the retention time of diphenhydramine**System suitability**[NOTE—See *Table 2* for the relative retention times.]**Sample:** *System suitability solution***Suitability requirements****Resolution:** NLT 2.0 between diphenhydramine related compound A and diphenhydramine**Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Diphenhydramine Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

 r_U = peak response of each impurity from the *Sample solution* r_S = peak response of diphenhydramine from the *Standard solution* C_S = concentration of USP Diphenhydramine Hydrochloride RS in the *Standard solution* (mg/mL) C_U = concentration of Diphenhydramine Hydrochloride in the *Sample solution* (mg/mL) F = relative response factor (see *Table 2*)**Acceptance criteria:** See *Table 2*. [NOTE—Disregard peaks that are less than 0.05% of the diphenhydramine peak.]**Table 2**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Diphenhydramine related compound A ^a	0.9	1.0	0.5
Diphenhydramine	1.0	—	—
4-Methyldiphenhydramine ^b	1.5	1.0	0.3
4-Bromodiphenhydramine ^c	1.8	1.0	0.3
Benzhydrol ^d	2.6	1.4	0.3

^a 2-(Diphenylmethoxy)-N-methylethanamine.^b 2-[(RS)-(4-Methylphenyl)phenylmethoxy]-N,N-dimethylethanamine.^c 2-[(RS)-(4-Bromophenyl)phenylmethoxy]-N,N-dimethylethanamine.^d Diphenylmethanol.^e Diphenylmethanone.

Table 2 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzophenone ^e	5.1	1.0	0.3
Any other unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

^a 2-(Diphenylmethoxy)-N-methylethanamine.^b 2-[(RS)-(4-Methylphenyl)phenylmethoxy]-N,N-dimethylethanamine.^c 2-[(RS)-(4-Bromophenyl)phenylmethoxy]-N,N-dimethylethanamine.^d Diphenylmethanol.^e Diphenylmethanone.

■1S (USP36)

SPECIFIC TESTS**• ACIDITY OR ALKALINITY****Sample solution:** 50 mg/mL of Diphenhydramine Hydrochloride in carbon dioxide-free water**Analysis:** To 10 mL of the *Sample solution*, add 0.15 mL of methyl red TS 2 and 0.25 mL of 0.01 N hydrochloric acid. The solution is pink. Titrate with 0.01 N sodium hydroxide.**Acceptance criteria:** NMT 0.5 mL of 0.01 N sodium hydroxide is required to change the color of the solution to yellow.**• LOSS ON DRYING <731>****Sample:** Dry a sample at 105° for 3 h.**Acceptance criteria:** NMT 0.5%**ADDITIONAL REQUIREMENTS**

- PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at room temperature.

Change to read:**• USP REFERENCE STANDARDS <11>**

USP Diphenhydramine Hydrochloride RS

■ USP Diphenhydramine Related Compound A RS
2-(Diphenylmethoxy)-N-methylethanamine hydrochloride.C₁₆H₁₉NO · HCl 277.79 ■1S (USP36)**Add the following:****•Dorzolamide Hydrochloride Ophthalmic Solution****DEFINITION**

Dorzolamide Hydrochloride Ophthalmic Solution is a sterile, isotonic, buffered, slightly viscous, aqueous solution of Dorzolamide Hydrochloride. It contains an amount of Dorzolamide Hydrochloride (C₁₀H₁₆N₂O₄S₃ · HCl) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of dorzolamide (C₁₀H₁₆N₂O₄S₃). It may contain a suitable preservative.

IDENTIFICATION**• A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST <201>****Standard solution:** 5.0 mg/mL of USP Dorzolamide Hydrochloride RS in methanol**Sample solution:** Equivalent to 5.0 mg/mL of dorzolamide from Ophthalmic Solution in methanol**Adsorbent:** 0.25-mm layer of chromatographic silica gel mixture or equivalent**Application volume:** 20 µL**Developing solvent system:** Methylene chloride, methanol, and ammonium hydroxide (80:20:1)**Analysis:** Spot the *Standard solution* and *Sample solution* approximately 2 cm from the bottom of the plate.

Evaporate the solvent using a current of air. Saturate the developing tank with the *Developing solvent system*, and equilibrate for approximately 1 h prior to use. Develop the chromatogram in the *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing tank, and allow the plate to air-dry in a fume hood. Examine the plate under short-wavelength UV light at 254 nm, or expose to iodine vapors.

Acceptance criteria: The R_f value of the principal spot from the *Sample solution* corresponds to that from the *Standard solution*.

- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**• PROCEDURE****Buffer:** Fill a 1-L volumetric flask approximately two-thirds full of water. Add 2.0 mL of phosphoric acid, and dilute with water to 900 mL. Adjust with triethylamine to a pH of 3.0, and dilute with water to volume.**Mobile phase:** Acetonitrile and *Buffer* (5:95)**Standard solution:** 0.11 mg/mL of USP Dorzolamide Hydrochloride RS and 0.5 µg/mL each of USP Dorzolamide Related Compound B RS and USP Dorzolamide Related Compound D RS in *Mobile phase***Sample solution:** Equivalent to 0.1 mg/mL of dorzolamide from Ophthalmic Solution in *Mobile phase***Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 253 nm**Column:** 4.6-mm × 25-cm; 5-µm packing L7**Flow rate:** 1 mL/min**Injection volume:** 20 µL**System suitability****Sample:** *Standard solution*[NOTE—See *Table 1* for the relative retention times.]**Suitability requirements****Resolution:** NLT 3.0 between dorzolamide and dorzolamide related compound D; and NLT 3.0 between dorzolamide and dorzolamide related compound B**Tailing factor:** NMT 1.8 for the dorzolamide peak**Relative standard deviation:** NMT 2.0% for the dorzolamide peak**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of dorzolamide (C₁₀H₁₆N₂O₄S₃) in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

 r_U = peak response of dorzolamide from the *Sample solution* r_S = peak response of dorzolamide from the *Standard solution* C_S = concentration of USP Dorzolamide Hydrochloride RS in the *Standard solution* (mg/mL) C_U = nominal concentration of dorzolamide in the *Sample solution* (mg/mL) M_{r1} = molecular weight of dorzolamide, 324.44 M_{r2} = molecular weight of dorzolamide hydrochloride, 360.90

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• ORGANIC IMPURITIES

Mobile phase, Standard solution, Sample solution, and System suitability: Proceed as directed in the Assay.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Proceed as directed in the Assay. In addition the run time is at least 1.4 times the retention time of dorzolamide.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dorzolamide related compound D in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of dorzolamide related compound D from the *Sample solution*

r_S = peak area of dorzolamide related compound D from the *Standard solution*

C_S = concentration of USP Dorzolamide Related Compound D RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of dorzolamide in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of dorzolamide, 324.44

M_{r2} = molecular weight of dorzolamide related compound D, 332.85

Calculate the percentage of dorzolamide related compound B in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of dorzolamide related compound B from the *Sample solution*

r_S = peak area of dorzolamide related compound B from the *Standard solution*

C_S = concentration of USP Dorzolamide Related Compound B RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of dorzolamide in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of dorzolamide, 324.44

M_{r2} = molecular weight of dorzolamide related compound B, 360.90

Calculate the percentage of each individual unspecified impurity in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area of each impurity from the *Sample solution*

r_S = peak area of dorzolamide from the *Standard solution*

C_S = concentration of USP Dorzolamide Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of dorzolamide in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of dorzolamide, 324.44

M_{r2} = molecular weight of dorzolamide hydrochloride, 360.90

Acceptance criteria

Individual impurities: See Table 1.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Dorzolamide related compound D ^a	0.87	0.5
Dorzolamide	1.00	—
Dorzolamide related compound B ^b	1.14	2.0
Total impurities ^c	—	3.0

^a (4S,6S)-4-Amino-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

^b (4R,6SR)-4-(Ethylamino)-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

^c The sum of dorzolamide related compound D, dorzolamide related compound B, and all unspecified impurities.

SPECIFIC TESTS

• **STERILITY TESTS** <71>: Meets the requirements

• **PH** <791>: 5.4–5.9

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers protected from light, at controlled room temperature.

• **USP REFERENCE STANDARDS** <11>

USP Dorzolamide Hydrochloride RS

USP Dorzolamide Related Compound B RS

(4R,6S)-4-(Ethylamino)-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

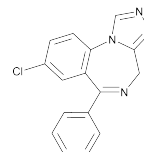
C₁₀H₁₆N₂O₄S₃ · HCl 360.90

USP Dorzolamide Related Compound D RS

(4S,6S)-4-Amino-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

C₈H₁₂N₂O₄S₃ · HCl 332.85 ■_{1S} (USP36)

Estazolam



C₁₆H₁₁ClN₄ 294.74

4H-[1,2,4]Triazolo[4,3-a][1,4]benzodiazepine, 8-chloro-6-phenyl-

8-Chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine [29975-16-4].

DEFINITION

Estazolam contains NLT 98.0% and NMT 102.0% of estazolam (C₁₆H₁₁ClN₄), calculated on the dried basis.

IDENTIFICATION

• **A. INFRARED ABSORPTION** <197K>

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

• PROCEDURE

Buffer: 2.8 g/L of monobasic potassium phosphate in water. Adjust with 1 N sodium hydroxide to a pH of 6.5.

Mobile phase: Acetonitrile, methanol, and *Buffer* (10:35:55)

Standard stock solution: 0.5 mg/mL of USP Estazolam RS in *Mobile phase*

Standard solution: 0.02 mg/mL of USP Estazolam RS in water from *Standard stock solution*

Sample stock solution: 0.5 mg/mL of Estazolam in *Mobile phase*

Sample solution: 0.02 mg/mL of Estazolam in water from *Sample stock solution*

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3-μm packing L11

Flow rate: 1 mL/min

Injection volume: 25 μL

Run time: 2.5 times the retention time of the estazolam peak

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of estazolam ($C_{16}H_{11}ClN_4$) in the portion of Estazolam taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Estazolam RS in the *Standard solution* (mg/mL)

C_U = concentration of Estazolam in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **RESIDUE ON IGNITION** ⟨281⟩: NMT 0.1%

• **HEAVY METALS**, *Method II* ⟨231⟩: NMT 20 ppm

Add the following:

• ORGANIC IMPURITIES

Solution A: Acetonitrile

Solution B: Water

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	40	60
20	90	10
23	90	10
30	40	60
35	40	60

System suitability solution: 1 μg/mL each of USP Estazolam RS, USP Nordazepam RS, and USP Estazolam Related Compound A RS in acetonitrile

Standard solution: 1 μg/mL of USP Estazolam RS in acetonitrile

Sample solution: 1 mg/mL of Estazolam in acetonitrile

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3-μm packing L1

Flow rate: 1 mL/min

Injection volume: 20 μL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between nordazepam and estazolam related compound A, *System suitability solution*

Tailing factor: NMT 1.2 for estazolam, *Standard solution*

Relative standard deviation: NMT 2.0% for estazolam, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Estazolam taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of estazolam from the *Standard solution*

C_S = concentration of USP Estazolam RS in the *Standard solution* (μg/mL)

C_U = concentration of Estazolam in the *Sample solution* (μg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. [NOTE—The gradient was established on an HPLC system with a dwell volume of approximately 1.0 mL. The injection time can be adjusted relative to the start of a run to accommodate changes in dwell volume from one HPLC system to another to achieve the separation desired.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Estazolam	1.0	—	—
Nordazepam	1.4	1.3	0.1
Estazolam related compound A	1.6	1.0	0.1
Formamido chlorobenzophenone ^a	2.0	1.5	0.1
Bischloroacetylbenzophenone ^b	2.2	1.5	0.1
Aminochlorobenzophenone ^c	2.6	1.4	0.1
Chloroacetamido chlorobenzophenone ^d	2.7	1.2	0.1
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.5

^a N-(2-Benzoyl-4-chlorophenyl) formamide.

^b 2-(N-Chloroacetyl-N-chloroacetylhydrazonomethyl)amino-5-chlorobenzophenone.

^c (2-Amino-5-chlorophenyl) phenyl-methanone.

^d N-(2-Benzoyl-4-chlorophenyl)-2-chloroacetamide.

■1S (USP36)

SPECIFIC TESTS

• LOSS ON DRYING ⟨731⟩

Analysis: Dry a sample at 105° for 4 h.

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

Change to read:**• USP REFERENCE STANDARDS <11>**

USP Estazolam RS

■ USP Estazolam Related Compound A RS

5-Chloro-2-(3-chloromethyl-4*H*-1,2,4-triazol-4-yl)-benzophenone.C₁₆H₁₁Cl₂N₃O 332.18

USP Nordazepam RS

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one.C₁₅H₁₁ClN₂O 270.71 ■_{1S} (USP36)**Delete the following:****• Estradiol Pellets****DEFINITION**

Estradiol Pellets are sterile pellets composed of Estradiol in compressed form, without the presence of any binder, diluent, or excipient. They contain NLT 97.0% and NMT 103.0% of estradiol (C₁₈H₂₄O₂).

IDENTIFICATION**• A. INFRARED ABSORPTION <197M>****• B. ULTRAVIOLET ABSORPTION <197U>**

Analytical wavelength: 280 nm

Sample: 50 µg/mL in alcohol

Acceptance criteria: Absorptivities do not differ by more than 3.0%

ASSAY**• PROCEDURE**

[NOTE—The *Standard solution*, *Sample solution* and *Blank solution* should be prepared and analyzed concomitantly]

Standard stock solution: 40 µg/mL of USP Estradiol RS in methanol

Standard solution: Transfer 1.0 mL of the *Standard stock solution* to a glass-stoppered, 16- × 150-mm test tube, and evaporate with the aid of gentle heat and a current of air to dryness. Using a suitable syringe, add 1.0 mL of iron-phenol TS. Suspend the tube in a vigorously boiling water bath, and mix after heating for 5 min. Remove the tube after heating in the water bath for a total of 35 min, and immediately cool in an ice-water bath. Remove from the ice bath, add 10.0 mL of dilute sulfuric acid (1 in 3) to obtain a homogeneous solution, and allow to reach room temperature.

Sample stock solution: Nominally 20 mg/mL of estradiol, prepared as follows. Dissolve 100 mg of estradiol from powdered Pellets (NLT 10) in 5 mL of alcohol and chloroform (1:1)

Sample solution: Transfer 1.0 mL of the *Sample stock solution* to a glass-stoppered, 16- × 150-mm test tube, and proceed as directed under *Standard solution*

Blank solution: Using a suitable syringe, add 1.0 mL of iron-phenol TS to a glass-stoppered, 16- × 150-mm test tube, and proceed as directed under *Standard solution*

Spectrometric conditions

(See *Spectrophotometry and Light-Scattering* <851>.)

Mode: UV-Vis

Analytical wavelength: 520 nm

Cell: 1 cm

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of estradiol (C₁₈H₂₄O₂) in the portion of Pellets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Estradiol RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–103.0%

PERFORMANCE TESTS**• WEIGHT VARIATION <905>**

Analysis: Weigh 5 Pellets singly, and calculate the average weight. The average weight is between 95% and 105% of the labeled weight of C₁₈H₂₄O₂, and each Pellet weighs 90%–110% of the labeled weight of C₁₈H₂₄O₂.

IMPURITIES**• CHROMATOGRAPHIC PURITY**

Mobile Phase: 2,2,4-trimethylpentane, n-butyl chloride and methanol (45:4:1)

Diluent: n-butyl chloride and methanol (5:1)

Sample solution: 0.7 mg/mL of estradiol in *Diluent*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; packing L3

Flow rate: 2 mL/min

Injection size: 10 µL

System suitability

Samples: *Sample solution*

Suitability requirements

Resolution: NLT 1.0 between estradiol and any other impurity

Column efficiency: NLT 800 theoretical plates

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Sample solution*

Calculate the percentage of each impurity in the portion of estradiol pellets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_T = sum of all peak responses from the *Sample solution*

Acceptance criteria: NMT 0.5% of any individual impurity, and NMT 1.0% total impurities are found

• SOLUBILITY IN CHLOROFORM: A 2.5 mg/mL solution from Pellets in chloroform is clear and practically free from insoluble residue**SPECIFIC TESTS****• MELTING RANGE OR TEMPERATURE <741>:** 173°–179°

[NOTE—Dry over silica gel NLT 16 h prior to testing]

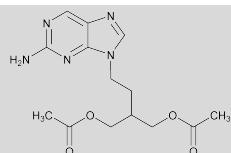
• OPTICAL ROTATION, Specific Rotation <781S>

Sample solution: 10 mg/mL in dioxane

Acceptance criteria: 76°–83°

• WATER, Method I, <921>: NMT 3.5%**• STERILITY TESTS <71>:** Meet the requirements**ADDITIONAL REQUIREMENTS****• PACKAGING AND STORAGE:** Preserve in tight containers, suitable for maintaining sterile contents, that hold 1 Pellet each.**• USP REFERENCE STANDARDS <11>**

USP Estradiol RS ■_{1S} (USP36)

Add the following:**•Famciclovir**

$C_{14}H_{19}N_5O_4$ 321.33
 1,3-Propanediol, 2-[2-(2-amino-9H-purin-9-yl)ethyl]-, diacetate (ester);
 2-[2-(2-Amino-9H-purin-9-yl)ethyl]-1,3-propanediol diacetate (ester) [104227-87-4].

DEFINITION

Famciclovir contains NLT 98.0% and NMT 102.0% of famciclovir ($C_{14}H_{19}N_5O_4$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**• PROCEDURE**

Dilute acid: Dilute 5 mL of phosphoric acid with water to 50 mL.

Diluent: Water

Buffer: 2.72 g/L of monobasic potassium phosphate in water. Adjust with *Dilute acid* to a pH of 4.0 ± 0.05 .

Mobile phase: Acetonitrile and *Buffer* (35:65)

Standard solution: 25 µg/mL of USP Famciclovir RS in *Diluent*

Sample solution: 25 µg/mL of Famciclovir in *Diluent*

Chromatographic system
 (See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 5 times the retention time of famciclovir

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2500 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of famciclovir ($C_{14}H_{19}N_5O_4$) in the portion of Famciclovir taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of the *Sample solution*
 r_S = peak response of the *Standard solution*
 C_S = concentration of USP Famciclovir RS in the *Standard solution* (mg/mL)
 C_U = concentration of Famciclovir in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **HEAVY METALS**, *Method II* (231): NMT 20 µg/g

• **ORGANIC IMPURITIES**

Dilute acid, Buffer, and Diluent: Proceed as directed in the *Assay*.

Solution A: *Buffer*

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
35	70	30
40	70	30
42	95	5
50	95	5

System suitability solution: 0.5 mg/mL of USP

Famciclovir System Suitability Mixture RS in *Diluent*

Standard solution: 0.5 µg/mL of USP Famciclovir RS, 1 µg/mL of USP Famciclovir Related Compound A RS, and 3 µg/mL of USP Famciclovir Related Compound B RS in *Diluent*

Sample solution: 500 µg/mL of Famciclovir in *Diluent*.

[NOTE—The solution is stable for 15 h at 6°.]

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between the propionyl famciclovir and 6-chloro famciclovir peaks, *System suitability solution*

Tailing factor: NMT 1.5 for the famciclovir peak, *System suitability solution*

Column efficiency: NLT 20,000 theoretical plates for the famciclovir peak, *System suitability solution*

Relative standard deviation: NMT 5.0% for the famciclovir peak; NMT 10.0% for the famciclovir related compound A and B peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Famciclovir taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of famciclovir from the *Standard solution*

C_S = concentration of USP Famciclovir RS in the *Standard solution* (µg/mL)

C_U = concentration of Famciclovir in the *Sample solution* (µg/mL)

F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dimethylaminopyridine ^a	0.12	0.59	0.05
Penciclovir ^b	0.16	0.29	0.50
Famciclovir related compound A ^c	0.19	1.3	0.20
Famciclovir related compound B ^d	0.51	1.1	0.60
N-7 Isomer of famciclovir ^e	0.89	0.92	0.10
Famciclovir	1.0	—	—
N-Acetyl famciclovir ^f	1.05	0.56	0.10
Deoxychloro famciclovir ^g	1.26	0.87	0.20
Propionyl famciclovir ^h	1.32	0.88	0.15
6-Chloro famciclovir ⁱ	1.36	0.85	0.15
6-Alkylamino famciclovir ^j	1.83	0.46	0.10
Any other unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

^a N,N-Dimethylpyridin-4-amine.^b 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine.^c 2-[2-(2-Amino-9H-purin-9-yl)ethyl]propane-1,3-diol.^d 4-(2-Amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl acetate.^e 2-[2-(2-Amino-7H-purin-7-yl)ethyl]propane-1,3-diyl diacetate.^f 2-[2-(2-Acetamido-9H-purin-9-yl)ethyl]propane-1,3-diyl diacetate.^g 4-(2-Amino-9H-purin-9-yl)-2-(chloromethyl)butyl acetate.^h 2-(Acetoxymethyl)-4-(2-amino-9H-purin-9-yl)butyl propionate.ⁱ 2-[2-(2-Amino-6-chloro-9H-purin-9-yl)ethyl]propane-1,3-diyl diacetate.^j 2-[2-(6-[4-Acetoxy-3-(acetoxymethyl)butylamino]-2-amino-9H-purin-9-yl)ethyl]propane-1,3-diyl diacetate.**SPECIFIC TESTS**• **LOSS ON DRYING** (731)

Analysis: Dry in vacuum at a pressure not exceeding 20 mm of mercury at 60° for 2 h.

Acceptance criteria: NMT 0.5%

• **RESIDUE ON IGNITION** (281): NMT 0.1%**ADDITIONAL REQUIREMENTS**• **PACKAGING AND STORAGE:** Store in a well-closed container at controlled room temperature.• **USP REFERENCE STANDARDS** (11)

USP Famciclovir RS

USP Famciclovir Related Compound A RS

[2-[2-(2-Amino-9H-purin-9-yl)ethyl]propane-1,3-diol] hydrochloride.

C₁₀H₁₅N₅O₂ · HCl 273.72

USP Famciclovir Related Compound B RS

4-(2-Amino-9H-purin-9-yl)-2-(hydroxymethyl)butyl acetate.

C₁₂H₁₇N₅O₃ 279.30

USP Famciclovir System Suitability Mixture RS

Contains famciclovir, propionyl famciclovir, and 6-chloro famciclovir. • (RB 1-Feb-2013)

Add the following:

Fluconazole for Oral Suspension**DEFINITION**Fluconazole for Oral Suspension contains NLT 90.0% and NMT 110.0% of the labeled amount of fluconazole (C₁₃H₁₂F₂N₆O). It may contain a suitable preservative.**IDENTIFICATION**

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY• **PROCEDURE****Diluted phosphoric acid:** Phosphoric acid (1 in 10)**Buffer:** 2.72 g/L of monobasic potassium phosphate, adjusted with *Diluted phosphoric acid* to pH 2.5**Mobile phase:** Acetonitrile and *Buffer* (20:80)**Diluent:** Methanol and water (50:50)**System suitability solution:** 0.1 mg/mL of USP Fluconazole RS and 0.024 mg/mL of USP Sodium Benzoate RS in *Diluent***Standard solution:** 0.1 mg/mL of USP Fluconazole RS in *Diluent***Sample solution:** Reconstitute the sample as directed on the label. Transfer an accurately weighed quantity of the suspension to a suitable volumetric flask to obtain a nominal concentration of 0.1 mg/mL of fluconazole. Sonicate in 70% of the flask volume of *Diluent* for 20 min with intermittent shaking. Dilute with *Diluent* to final volume, mix, centrifuge, and pass through a suitable membrane filter.**Chromatographic system**(See *Chromatography* (621), *System Suitability*.)**Mode:** LC**Detector:** 260 nm**Column:** 4.6-mm × 15.0-cm; 5-μm packing L1**Flow rate:** 1.5 mL/min**Injection volume:** 50 μL**System suitability****Sample:** *System suitability solution***Suitability requirements****Resolution:** NLT 5.0 between the fluconazole and benzoate peaks**Tailing factor:** NMT 2.0, fluconazole peak**Relative standard deviation:** NMT 2.0%, fluconazole peak**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of the labeled amount of fluconazole (C₁₃H₁₂F₂N₆O) in the portion of the Fluconazole for Oral Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response from the *Sample solution* r_S = peak response from the *Standard solution* C_S = concentration of the *Standard solution* C_U = nominal concentration of the *Sample solution*

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS• **DISSOLUTION** (711)**Medium:** Water; 900 mL for 200 mg/5 mL suspension; 500 mL for 50 mg/5 mL suspension**Apparatus 2:** 50 rpm**Time:** 30 min

Standard stock solution: 1.1 mg/mL of USP Fluconazole RS in methanol

Standard solution

200 mg/5 mL suspension: 0.22 mg/mL of USP Fluconazole RS in *Medium* from the *Standard stock solution*

50 mg/5 mL suspension: 0.11 mg/mL of USP Fluconazole RS in *Medium* from the *Standard stock solution*

Sample solution: Reconstitute the suspension according to the label instructions. Weigh, and transfer an amount of the reconstituted suspension equivalent to one dose to the vessel. At the time specified withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45- μ m pore size.

Mobile phase: Acetonitrile and water (20:80)

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 50 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Calculate the percentage of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) dissolved (Q):

$$\text{Result} = (r_U/r_S) \times C_S \times (V_1/V_2) \times (1/L) \times 100$$

r_U = peak response for the *Sample solution*

r_S = peak response for the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

V_1 = volume of *Medium* (900 mL or 500 mL)

V_2 = volume of the reconstituted suspension in the *Sample solution* (mL). [NOTE—This is equivalent to the weight (g) of the reconstituted suspension in the *Sample solution* divided by the density of the reconstituted solution (g/mL).]

L = label claim (mg/mL)

Tolerances: NLT 85% (Q) of the labeled amount of fluconazole ($C_{13}H_{12}F_2N_6O$) is dissolved.

- **DELIVERABLE VOLUME** (698): Meets the requirements for oral suspension packaged in multiple-unit containers

IMPURITIES

• **PROCEDURE**

Solution A: 0.63 g/L of ammonium formate in water

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	87	13
20	87	13
35	60	40
50	60	40
52	87	13
60	87	13

Diluent: Acetonitrile and *Solution A* (13:87)

System suitability solution: 0.3 mg/mL of USP Fluconazole RS, 3 μ g/mL of USP Fluconazole Related Compound B RS, and 3 μ g/mL of USP Fluconazole Re-

lated Compound C RS in *Diluent*. [NOTE—The use of sonication and stepwise dilutions may be appropriate.]

Standard solution: 6 μ g/mL of USP Fluconazole RS in *Diluent*. [NOTE—The use of sonication and stepwise dilutions may be appropriate.]

Sample solution: Reconstitute the sample as directed on the label. Transfer an accurately weighed quantity of the suspension to a suitable volumetric flask to obtain a nominal concentration of 3 mg/mL of fluconazole. Sonicate in 40% of the flask volume of *Diluent* for 20 min with intermittent shaking. Dilute with *Diluent* to final volume, mix, centrifuge, and pass through a suitable membrane filter.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: 260 nm

Column: 4.6-mm \times 12.5-cm; 3- μ m packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between the fluconazole related compound B and fluconazole related compound C peaks and NLT 4.0 between the fluconazole related compound C and fluconazole peaks, *System suitability solution*

Tailing factor: NMT 2.0 for the fluconazole peak, *System suitability solution*

Relative standard deviation: NMT 5.0% for the fluconazole peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Fluconazole for Oral Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of the impurity from the *Sample solution*

r_S = peak response of fluconazole from the *Standard solution*

C_S = concentration of USP Fluconazole RS in the *Standard solution*

C_U = nominal concentration of fluconazole the *Sample solution*

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fluconazole related compound A ^a	0.45	— ^b
Fluconazole isomer ^c	0.51	— ^b
Fluconazole related compound B ^d	0.71	— ^b
Fluconazole related compound C ^e	0.78	— ^b
Fluconazole	1.0	—

^a 2-[2-Fluoro-4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

^b These are process impurities which are included in the Table for identification only. These impurities are controlled in the drug substance. They are not to be reported for the drug product and should not be included in the total impurities.

^c 2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol.

^d 2-(4-Fluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

^e 1,1'-(1,3-Phenylene)di(1*H*-1,2,4-triazole).

Table 2 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any other individual, unspecified impurity	—	0.20
Total impurities	—	0.3

^a 2-[2-Fluoro-4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

^b These are process impurities which are included in the Table for identification only. These impurities are controlled in the drug substance. They are not to be reported for the drug product and should not be included in the total impurities.

^c 2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-(4*H*-1,2,4-triazol-4-yl)propan-2-ol.

^d 2-(4-Fluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

^e 1,1'-(1,3-Phenylene)di(1*H*-1,2,4-triazole).

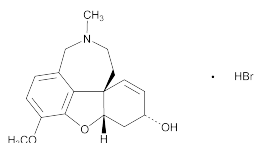
SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count does not exceed 10² cfu/g, and the total combined molds and yeasts count does not exceed 5 × 10¹ cfu/g. It meets the requirements of the test for absence of *Escherichia coli*.
- **PH** (791): 3.0–5.0, in a solution reconstituted as directed by the labeling

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Store dry powder below 30°. Store reconstituted suspension at 5°–30°, and protect from freezing.
- **USP REFERENCE STANDARDS** (11)
 - USP Fluconazole RS
 - USP Fluconazole Related Compound B RS
 - 2-(4-Fluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.
C₁₃H₁₃FN₆O 288.28
 - USP Fluconazole Related Compound C RS
 - 1,1'-(1,3-Phenylene)di(1*H*-1,2,4-triazole).
C₁₀H₈N₆ 212.21
 - USP Sodium Benzoate RS_{1S} (USP36)

Galantamine Hydrobromide



C₁₇H₂₁NO₃ · HBr 368.27
 6*H*-Benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol,
 4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-,
 hydrobromide, (4*a*5,6*R*,8*a*5)-;
 (4*a*5,6*R*,8*a*5)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-
 11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol
 hydrobromide [1953-04-4].

DEFINITION

Galantamine Hydrobromide contains NLT 98.0% and NMT 102.0% of galantamine hydrobromide (C₁₇H₂₁NO₃ · HBr), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)

[NOTE—Specimens are to be prepared using undried USP Galantamine Hydrobromide RS and the test article.]

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL, Bromide** (191)

Sample solution: A solution of 7 mg/mL in water
Acceptance criteria: Meets the requirements of the silver nitrate precipitate test

ASSAY

Change to read:

PROCEDURE

Diluent: Methanol and water (1:19)

Buffer: 0.79 g/L of dibasic sodium phosphate dihydrate and 2.46 g/L of anhydrous monobasic sodium phosphate in water

Solution A: Methanol and *Buffer* (5:95)

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
6.0	100	0
20.0	95	5
35.0	85	15
50.0	80	20
51.0	40	60
55.0	40	60
56.0	100	0
60.0	100	0

System suitability solution: 1 mg/mL of USP Galantamine Hydrobromide Related Compounds Mixture RS in *Diluent*

Standard solution: 1.0 mg/mL of USP Galantamine Hydrobromide RS in *Diluent*

Sample solution: 1.0 mg/mL of Galantamine Hydrobromide in *Diluent*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 10-cm; 3.5-μm packing L1

Column temperature: 55°

Flow rate: 1.5 mL/min

Injection volume: 20 μL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—For relative retention times, see *Table 2*.]

Suitability requirements

Resolution: NLT 4.5 between galantamine and 6*α*-hexahydrogalantamine, *System suitability solution*

Tailing factor: NMT 2.0 for galantamine,

■_{1S} (USP36) *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of galantamine hydrobromide (C₁₇H₂₁NO₃ · HBr) in the portion of Galantamine Hydrobromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)

C_U = concentration of Galantamine Hydrobromide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%
- **HEAVY METALS**, *Method II* (231): NMT 20 ppm
- **LIMIT OF PALLADIUM**

[NOTE—Perform this test only if palladium is a known inorganic impurity of the manufacturing process.]

Standard stock solution: 20 mg/L of palladium reference stock solution (NIST traceable) in water

Aqua regia: Under a hood, carefully mix hydrochloric acid and nitric acid (3:1).

[NOTE—To obtain each of the required *Standard solutions*, it is recommended that the required volume of *Standard stock solution* be mixed with a volume of *Aqua regia* equivalent to 5% of the final volume, followed by water.]

Standard solution A: 0.2 mg/L of palladium from the *Standard stock solution* in water

Standard solution B: 1.0 mg/L of palladium from the *Standard stock solution* in water

Standard solution C: 2.0 mg/L of palladium from the *Standard stock solution* in water

System suitability solution: Prepare a solution having a known concentration of 1.6 mg/L of palladium, as directed for *Standard solutions*.

Sample solution: Weigh 1 g of Galantamine Hydrobromide. Transfer the sample to an appropriate digestion system, and digest using appropriate acids (e.g., nitric acid or mixtures of nitric acid and sulfuric acid and mixtures of nitric acid and hydrogen peroxide). After digestion, heat to dryness. Add 0.5 mL of *Aqua regia* and 2 mL of water. Warm gently to dissolve any residue. Allow to cool. Transfer quantitatively to a 10-mL volumetric flask, and dilute with water to volume.

Digestion blank solution: Prepare this solution following the procedure for the *Sample solution*, without the test article.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: Atomic absorption spectroscopy (flame)

Analytical wavelength: 247.6 nm (0.2-nm slit width)

Lamp: Palladium hollow-cathode

Blank solution: Dilute 5 mL of *Aqua regia* with water to 100 mL.

System suitability

Samples: *Standard solution A*, *Standard solution B*, *Standard solution C*, *System suitability solution*, and *Blank solution*

Using the *Standard solutions* and *Blank solution*, construct a calibration curve.

Suitability requirements

Correlation coefficient: NLT 0.99

Recovery: 87.5%–112.5%, *System suitability solution*. [NOTE—Recovery is calculated using the calibration curve.]

Analysis

Samples: *Sample solution* and *Digestion blank solution*

Calculate the concentration of palladium in the *Sample solution*, using the calibration curve, corrected for the *Digestion blank solution* and the sample weight. Calculate the amount of palladium in the Galantamine Hydrobromide taken to prepare the *Sample solution*.

Acceptance criteria: NMT 10 ppm

Change to read:

• ORGANIC IMPURITIES

Diluent, Buffer, Solution A, Solution B, Mobile phase, System suitability solution, Sample solution, Chromatographic system, and System suitability: Prepare as directed in the *Assay*.

Standard solution: 5.0 µg/mL of USP Galantamine Hydrobromide RS in *Diluent*

Analysis

Samples: *Sample solution* and *Standard solution*

[NOTE—Ignore the peak due to bromide near the void volume and any peak below 0.05%.]

Calculate the percentage of each impurity in the portion of Galantamine Hydrobromide taken, on the dried basis:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (100/100 - L)$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of galantamine from the *Standard solution*

C_S = concentration of USP Galantamine Hydrobromide RS in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

L = loss on drying in percent

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
■N-Desmethyl galantamine ^a ■ _{1S} (USP36)	0.29	1.2	0.6
■O-Desmethyl galantamine ^b ■ _{1S} (USP36)	0.35	1.1	0.20
■Galantamine N-oxide ^c ■ _{1S} (USP36)	0.65	0.96	0.20
■Dihydrogalantamine ^d ■ _{1S} (USP36)	0.82	0.81	0.35
Galantamine ■ _{1S} (USP36)	1.00	1.0	—
■6S-Galantamine ^e ■ _{1S} (USP36)	1.16	0.95	0.20
Narwedine ^f	1.64	1.9	0.15
■Didehydrodeoxygalantamine ^g ■ _{1S} (USP36)	2.05	1.2	0.40

^a (4aS,6R,8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol.

^b (4aS,6R,8aS)-4a,5,9,10,11,12-Hexahydro-3-hydroxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol.

^c ■(4aS,6R,8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol, N-oxide; also known as 6β-hexahydrogalantamine.■_{1S} (USP36)

^d ■(4aS,6R,8aS)-4a,5,7,8,9,10,11,12-Octahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol; also known as 6β-octahydrogalantamine.■_{1S} (USP36)

^e ■(4aS,6S,8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol; also known as 6α-Hexahydrogalantamine or epi-galantamine.■_{1S} (USP36)

^f (4aS,8aS)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-one. [NOTE—This is a process impurity that may be found in galantamine hydrobromide isolated from a natural source.]

^g ■(4aS,8aS)-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepine; also known as tetrahydrogalantamine.■_{1S} (USP36)

^h Do not include the 4R,8R-stereoisomer.

Table 2 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any unspecified impurity	—	1.0	0.10
Total impurities ^h	—	—	1.0

^a (4*a*S,6*R*,8*a*S)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol.

^b (4*a*S,6*R*,8*a*S)-4*a*,5,9,10,11,12-Hexahydro-3-hydroxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol.

^c ■(4*a*S,6*R*,8*a*S)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol, *N*-oxide; also known as 6β-hexahydrogalantamine. ■_{1S} (USP36)

^d ■(4*a*S,6*R*,8*a*S)-4*a*,5,7,8,9,10,11,12-Octahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol; also known as 6β-octahydrogalantamine. ■_{1S} (USP36)

^e ■(4*a*S,6*S*,8*a*S)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol; also known as 6α-Hexahydrogalantamine or *epi*-galantamine. ■_{1S} (USP36)

^f (4*a*S,8*a*S)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one. [NOTE—This is a process impurity that may be found in galantamine hydrobromide isolated from a natural source.]

^g ■(4*a*S,8*a*S)-9,10,11,12-Tetrahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepine; also known as tetrahydrogalantamine. ■_{1S} (USP36)

^h Do not include the 4*R*,8*R*-stereoisomer.

Change to read:

• ENANTIOMERIC PURITY

[NOTE—If Galantamine Hydrobromide is not isolated from a natural source, perform either *Procedure 1* or *Procedure 2*.]

Procedure 1

Background electrolyte solution: 8.9 g/L of dibasic sodium phosphate dihydrate in water. Adjust with phosphoric acid to a pH of 3.0.

Run buffer: 19.6 g/L of α-cyclodextrin hydrate in *Background electrolyte solution*. Pass the solution through a filter of 0.22-μm pore size.

Standard solution: 5 μg/mL of USP Galantamine Hydrobromide Racemic RS in water. Pass the solution through a filter of 0.22-μm pore size, discarding the first 8 mL.

Sample solution: 0.5 mg/mL of Galantamine Hydrobromide in water. Pass the solution through a filter of 0.22-μm pore size, discarding the first 8 mL.

Capillary rinse procedure: Use separate *Run buffer* vials for the capillary rinse and sample analysis. Proceed as directed in *Table 3*.

Table 3

Step #	Solution/Gas	Time (min)
1	0.1 N sodium hydroxide	15
2	Water	10
3	Suitable gas	5

[NOTE—If a new or dry capillary is being used, rinse with 1 N sodium hydroxide for 30 min, followed by rinsing with water for 15 min. Dry it with air or nitrogen for 10 min.]

Electrophoretic system

■_{1S} (USP36)

Mode: CE

Detector: UV 214 nm

Column: 75-μm × 60-cm uncoated fused-silica

Column temperature: 20°

Applied voltage: 250 V/cm, positive polarity

Run time: 35 min

System suitability

Sample: *Standard solution*. [NOTE—For the purpose of identification, the 4*S*,8*S* stereoisomer elutes at an approximate relative migration time (RMT) of 1.00, and the 4*R*,8*R* stereoisomer elutes at an RMT of about 1.05.]

Suitability requirements

Resolution: NLT 2.5 between the two enantiomers

Relative standard deviation: NMT 10% for the 4*R*,8*R* stereoisomer peak

Measure the migration times and peak responses: the migration times for the 4*R*,8*R* stereoisomer in the electropherograms for the *Sample solution* should not deviate by more than 5% of the migration time for the same component in the electropherogram of the *Standard solution*.

Analysis

Samples: *Standard solution* and *Sample solution*

Injection: [NOTE—Rinse the capillary between injections as follows: water for 5 min, followed by *Run buffer* for 5 min. Rinse times are based on a rinse pressure of 1.4 bar.]

Sample solution: 34.5 mbar for 4 s

Run buffer: 6.9 mbar for 5 s

Calculate the corrected peak responses using the formula:

$$\text{Result} = (r/m)$$

r = peak response

m = migration time of the peak (min)

Calculate the limit of the 4*R*,8*R* isomer, in percent, in the portion of Galantamine Hydrobromide taken:

$$\text{Result} = (r_{CU}/r_{CS}) \times (C_S/C_U) \times P \times 100$$

*r*_{CU} = average corrected peak responses for the 4*R*,8*R* isomer from the *Sample solution*

*r*_{CS} = average corrected peak responses for the 4*R*,8*R* isomer from the *Standard solution*

*C*_S = concentration of USP Galantamine Hydrobromide ■_{Racemic} ■_{1S} (USP36) RS in the *Standard solution* (mg/mL)

*C*_U = concentration of Galantamine Hydrobromide in the *Sample solution* (mg/mL)

P = chiral purity of USP Galantamine Hydrobromide Racemic RS, 0.5

Acceptance criteria: NMT 0.10% of the 4*R*,8*R* stereoisomer

Procedure 2

[NOTE—Use low-actinic glassware and vials. It is recommended that precautions be taken to protect all solutions from light.]

Buffer: 8.2 g/L of sodium acetate in water

Mobile phase: Acetonitrile and *Buffer* (2:98). Adjust with acetic acid to a pH of 6.5.

System suitability solution: ■2.4 μg/mL of USP Galantamine Hydrobromide Racemic RS in water. [NOTE—This solution will contain about 1.2 μg/mL of the 4*R*,8*R* stereoisomer.] ■_{1S} (USP36)

Sample solution: 1.2 mg/mL of Galantamine Hydrobromide in water

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.0-mm × 15-cm; 5-μm packing L41.

[NOTE—Alternatively a 2.0-mm × 15.0-cm column containing 5-μm L41 packing can be used with a recommended flow rate of about 0.2 mL/min.]

Flow rate: 0.8 mL/min

Injection volume: 5 μL

System suitability

Sample: *System suitability solution*. [NOTE—The 4*R*,8*R* stereoisomer elutes first as the minor peak followed by the major peak due to galantamine (which is the same as the 4*S*,8*S* stereoisomer).]

Suitability requirements

Resolution: NLT 3.0 between the 4*R*,8*R* stereoisomer and galantamine peaks

Relative standard deviation: NMT 5.0% for the 4*R*,8*R* stereoisomer peak

Analysis

Sample: *Sample solution*

Calculate the percentage of 4*R*,8*R* stereoisomer in the portion of Galantamine Hydrobromide taken:

$$\text{Result} = 100 \times [r_{4R,8R} / (r_{4R,8R} + r_{4S,8S})]$$

$r_{4R,8R}$ = peak area of the 4*R*,8*R* stereoisomer from the *Sample solution*

$r_{4S,8S}$ = peak area of the galantamine peak from the *Sample solution*

Acceptance criteria: NMT 0.10% of the 4*R*,8*R* stereoisomer

SPECIFIC TESTS

• **LOSS ON DRYING** (731)

Analysis: Dry a sample at 105° for 4 h.

Acceptance criteria: NMT 0.5%

• **OPTICAL ROTATION, Specific Rotation** (781)

[NOTE—If Galantamine Hydrobromide is isolated from a natural source, perform the test for *Optical Rotation*.]

Sample solution: 20 mg/mL in water

Acceptance criteria: −90° to −100°

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Store at room temperature. Preserve in well-closed containers.

• **LABELING:** Label it to state if the source is naturally derived or is synthetic. If the source is not natural, perform either *Procedure 1* or *Procedure 2* of the test for *Enantiomeric Purity*. If the source is natural, perform the test for *Optical Rotation* (781), *Specific Rotation*.

• **USP REFERENCE STANDARDS** (11)

USP Galantamine Hydrobromide RS

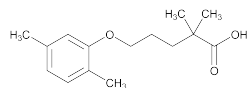
USP Galantamine Hydrobromide Racemic RS

A 50:50 mixture of 4*S*,8*S* and 4*R*,8*R* isomers.

USP Galantamine Hydrobromide Related Compounds Mixture RS

Contains galantamine hydrobromide, 6β-hexahydrogalantamine, 6β-octahydrogalantamine, 6α-hexahydrogalantamine, and tetrahydrogalantamine.

Gemfibrozil



C₁₅H₂₂O₃

250.33

Pentanoic acid, 5-(2,5-dimethylphenoxy)-2,2-dimethyl-;
2,2-Dimethyl-5-(2,5-xyliloxy)valeric acid [25812-30-0].

DEFINITION

Gemfibrozil contains NLT 98.0% and NMT 102.0% of gemfibrozil (C₁₅H₂₂O₃), calculated on the anhydrous basis.

IDENTIFICATION

• **A. INFRARED ABSORPTION** (197K)

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■1S (USP36)

ASSAY

Change to read:

• **PROCEDURE**

Mobile phase: Add 10 mL of glacial acetic acid to 800 mL of methanol in a 1000-mL volumetric flask, dilute with water to volume, and pass through a membrane filter.

System suitability solution: 0.2 mg/mL of gemfibrozil and 0.05 mg/mL of ■2,5-dimethylphenol■1S (USP36) in *Mobile phase*

Standard stock solution: 1 mg/mL of USP Gemfibrozil RS in methanol

Standard solution: 0.2 mg/mL of USP Gemfibrozil RS in *Mobile phase* from the *Standard stock solution*

Sample stock solution: 1 mg/mL of Gemfibrozil in methanol

Sample solution: 0.2 mg/mL of Gemfibrozil in *Mobile phase* from the *Sample stock solution*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 276 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 0.8 mL/min

Injection volume: 10 μL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

■[NOTE—The elution order is 2,5-dimethylphenol, followed by gemfibrozil.]■1S (USP36)

Resolution: NLT 8.0 between gemfibrozil and ■2,5-dimethylphenol,■1S (USP36) *System suitability solution*

Relative standard deviation: ■NMT 1.0%,■1S (USP36) *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of gemfibrozil (C₁₅H₂₂O₃) in the portion of Gemfibrozil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Gemfibrozil RS in the *Standard solution* (mg/mL)

C_U = concentration of Gemfibrozil in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

• **HEAVY METALS, Method II** (231): NMT 20 ppm

Change to read:

• **ORGANIC IMPURITIES**

Mobile phase: Add 10 mL of glacial acetic acid to 750 mL of methanol in a 1000-mL volumetric flask, di-

lute with water to volume, and pass through a membrane filter.

Peak identification solution: \blacksquare_{1S} (USP36) 0.2 mg/mL of USP Gemfibrozil RS, 0.05 mg/mL of USP Gemfibrozil Related Compound A RS, and 0.05 mg/mL of 2,5-dimethylphenol in *Mobile phase*

Standard stock solution: 0.1 mg/mL each of USP Gemfibrozil RS and USP Gemfibrozil Related Compound A RS in methanol

Standard solution: 0.01 mg/mL each of USP Gemfibrozil RS and USP Gemfibrozil Related Compound A RS in *Mobile phase* from the *Standard stock solution*

Sample solution: 10 mg/mL of Gemfibrozil in *Mobile phase*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 276 nm

Column: 4.0-mm \times 25-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 100 μ L

System suitability

Sample: $\blacksquare_{Standard\ solution}$ \blacksquare_{1S} (USP36)

\blacksquare_{1S} (USP36)

Suitability requirements

Relative standard deviation: NMT 3.0% $\blacksquare_{for\ each\ peak}$ \blacksquare_{1S} (USP36)

Analysis

$\blacksquare_{Chromatograph\ the\ Peak\ identification\ solution, and\ identify\ the\ components\ on\ the\ basis\ of\ their\ relative\ retention\ times. The\ relative\ retention\ times\ for\ 2,5-dimethylphenol, gemfibrozil, and gemfibrozil\ related\ compound\ A\ are\ 0.35, 1.0, and 2.1, respectively.}$

\blacksquare_{1S} (USP36)

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of gemfibrozil related compound A in the portion of Gemfibrozil taken:

$$Result = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of gemfibrozil related compound A from the *Sample solution*

r_S = peak area of gemfibrozil related compound A from the *Standard solution*

C_S = concentration of USP Gemfibrozil Related Compound A RS in the *Standard solution* (mg/mL)

C_U = concentration of Gemfibrozil in the *Sample solution* (mg/mL)

Calculate the percentage of any other impurity in the portion of Gemfibrozil taken:

$$Result = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of each individual impurity from the *Sample solution*

r_S = peak area for gemfibrozil from the *Standard solution*

C_S = concentration of USP Gemfibrozil RS in the *Standard solution* (mg/mL)

C_U = concentration of Gemfibrozil in the *Sample solution* (mg/mL)

Acceptance criteria

Gemfibrozil related compound A: NMT 0.1%

Any other impurity: NMT 0.1%

Total impurities: NMT 0.5%

SPECIFIC TESTS

Delete the following:

\blacksquare_{\bullet} **MELTING RANGE OR TEMPERATURE** <741>: 58°–61° \blacksquare_{1S} (USP36)

\bullet **WATER DETERMINATION, Method I** <921>: NMT 0.25%

ADDITIONAL REQUIREMENTS

\bullet **PACKAGING AND STORAGE:** Preserve in tight containers.

\bullet **USP REFERENCE STANDARDS** <11>

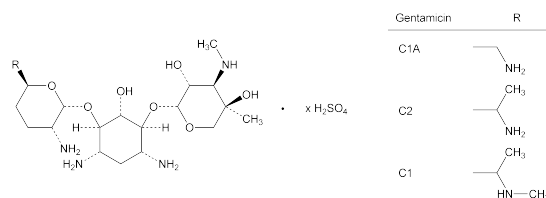
USP Gemfibrozil RS

USP Gemfibrozil Related Compound A RS

(*E,Z*)-2,2-Dimethyl-5-[2,5-dimethyl-4-(propene-1-yl)phenoxy]valeric acid.

$C_{18}H_{26}O_3$ 290.40

Gentamicin Sulfate



Gentamicin sulfate (salt);
Gentamycin sulfate [1405-41-0].

DEFINITION

Gentamicin Sulfate is the sulfate salt, or a mixture of such salts, of the antibiotic substances produced by the growth of *Micromonospora purpurea*. It has a potency equivalent to NLT 590 μ g/mg of gentamicin, calculated on the dried basis.

IDENTIFICATION

\bullet **A. INFRARED ABSORPTION** <197K>

\bullet **B. IDENTIFICATION TESTS—GENERAL, Sulfate** <191>

ASSAY

\bullet **PROCEDURE**

Analysis: Proceed as directed for Gentamicin under *Antibiotics—Microbial Assays* <81>.

Acceptance criteria: NLT 590 μ g/mg of gentamicin, calculated on the dried basis

IMPURITIES

\bullet **RESIDUE ON IGNITION** <281>: NMT 1.0%

Change to read:

\bullet **LIMIT OF METHANOL** $\blacksquare_{(if\ present)}$ \blacksquare_{1S} (USP36)

Internal standard solution: 0.50% v/v of *n*-propyl alcohol

Standard solution: 0.25% v/v each of methanol and *n*-propyl alcohol

Control solution: 250 mg/mL of Gentamicin Sulfate

Sample solution: 250 mg/mL of Gentamicin Sulfate in a mixture of *Internal standard solution* and water (1:1)

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 4-mm × 1.5-m; packed with support S3

Temperature

Column: Constant temperature between 120° and 140°

Injector: Constant temperature at least 50° higher than the column temperature

Detector: Constant temperature at least 50° higher than the column temperature

Carrier gas: Nitrogen

Flow rate: Constant flow rate between 30 and 40 mL/min

Injection type: Syringe with a polytetrafluoroethylene-tipped plunger

Injection volume: 2 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 1.0 between *n*-propyl alcohol and methanol

Analysis

Samples: *Standard solution*, *Sample solution*, and *Control solution*

Chromatograph the *Control solution*, and examine the chromatogram: if any peak is observed at a retention time corresponding to that of *n*-propyl alcohol, use the response of that peak to correct the *n*-propyl alcohol peak response of the *Sample solution*.

Calculate the percentage of methanol in the Gentamicin Sulfate taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times D \times F \times 100$$

R_U = peak area response of methanol to *n*-propyl alcohol (corrected for any peak at the locus of the *n*-propyl alcohol peak in the *Control solution*) from the *Sample solution*

R_S = peak area response of methanol to *n*-propyl alcohol from the *Standard solution*

C_S = percentage of methanol in the *Standard solution* (% v/v)

C_U = concentration of Gentamicin Sulfate in the *Sample solution* (mg/mL)

D = density of methanol (g/mL)

F = conversion factor, 0.001 g/mg

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

Change to read:

• CONTENT OF GENTAMICINS

Mobile phase: To 900 mL of carbonate-free water, add 7 mL of trifluoroacetic acid, 250 µL of pentafluoropropanoic acid, and 4 mL of 12.5 M sodium hydroxide (carbonate-free). Allow to equilibrate, and adjust with 0.5 M sodium hydroxide (carbonate-free) to a pH of 2.6. Add 15 mL of acetonitrile, and dilute with carbonate-free water to 1 L. If necessary, adjust the volume of acetonitrile in the *Mobile phase*. A total volume of up to 50 mL can be added per L of *Mobile phase*.

System suitability solution: 100 µg/mL of USP

Gentamicin Sulfate RS and 20 µg/mL of USP Sisomicin Sulfate RS in *Mobile phase*

Sample solution: 0.2 mg/mL of Gentamicin Sulfate in *Mobile phase*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: Pulsed amperometric electrochemical detector

Indicator electrode: Gold

Reference electrode: Silver-silver chloride

Auxiliary electrode: Stainless steel. [NOTE—If the cell body is made of stainless steel, it can be used as the auxiliary electrode.]

Waveform: See *Table 1*.

Table 1

Time (s)	Potential (V)	Integration
0.00	+0.05	—
0.10	+0.05	Begin
0.40	+0.05	End
0.41	+0.75	—
0.55	+0.75	—
0.56	−0.15	—
1.00	−0.15	—

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Post-column reagent: 20 g/L sodium hydroxide (carbonate-free), degassed and introduced pulselessly using a 375-µL polymeric mixing coil. [NOTE—A suitable mixing coil is the knitted reaction coil, part number 043700, available from Dionex Corporation (www.dionex.com).]

Flow rate of post-column reagent: 0.3 mL/min

Injection volume: 20 µL

Run time: 1.2 times the retention time of gentamicin C_1

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between gentamicin C_2 and gentamicin C_{2b}

Analysis

Sample: *Sample solution*

Calculate the percentage of each gentamicin in the portion of Gentamicin Sulfate taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak area response corresponding to the particular gentamicin

r_T = sum of the area responses of the gentamicin C_{1a} , gentamicin C_{2a} , gentamicin C_{2a} , gentamicin C_{2b} and gentamicin C_1 peaks

Acceptance criteria: Identify peaks by the relative retention times in *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Garamine ^{a,b}	0.35	—
Sisomicin ^{a,c}	1.0	—
Gentamicin C_{1a}	1.1	10%–35%
Gentamicin C_2	1.8	25%–55% ^d
Gentamicin C_{2a}	2.3	
Gentamicin C_{2b}	2.0	25%–50% ^e
Gentamicin C_1	2.9	

^a These compounds are listed for information only and are not to be reported in this test.

^b 4-O-[3-Deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl]-2-deoxy-L-streptamine.

^c O-3-Deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1→4)-O-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-glycero-hex-4-enopyranosyl-(1→6)]-2-deoxy-D-streptamine.

^d The limit is for the sum of gentamicin C_2 and gentamicin C_{2a} .

^e The limit is for the sum of gentamicin C_{2b} and gentamicin C_1 .

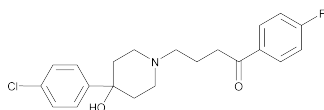
- **OPTICAL ROTATION**, *Specific Rotation* (781S)
Sample solution: 10 mg/mL
Acceptance criteria: +107° to +121°
- **PH** (791)
Sample solution: 40 mg/mL
Acceptance criteria: 3.5–5.5
- **LOSS ON DRYING** (731)
Analysis: Dry it in vacuum at a pressure NMT 5 mm of mercury at 110° for 3 h.
Acceptance criteria: NMT 18.0%
- **STERILITY TESTS** (71): Where the label states that Gentamicin Sulfate is sterile, it meets the requirements.
- **BACTERIAL ENDOTOXINS TEST** (85): Where the label states that Gentamicin Sulfate is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.71 USP Endotoxin Unit/mg of gentamicin.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

Change to read:

- **USP REFERENCE STANDARDS** (11)
USP Endotoxin RS
USP Gentamicin Sulfate RS
■ USP Sisomicin Sulfate RS ■^{1S} (USP36)

Haloperidol

$C_{21}H_{23}ClFNO_2$ 375.86
1-Butanone, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-;
4-[4-(p-Chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone [52-86-8].

DEFINITION

Haloperidol contains NLT 98.0% and NMT 102.0% of haloperidol ($C_{21}H_{23}ClFNO_2$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)

Change to read:

- **B.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the test for *Organic Impurities*. ■^{1S} (USP36)

ASSAY**Change to read:**

- **PROCEDURE**
Sample solution: 5 mg/mL of Haloperidol in glacial acetic acid

Titrimetric system

(See *Titrimetry* (541).)

Mode: Direct titration

Titrant: 0.05 N perchloric acid VS

Endpoint detection: Visual

Analysis: To 25 mL of the *Sample solution* add 3 drops of *p*-naphtholbenzein TS, and titrate with *Titrant*. Perform a blank determination, and make any necessary correction.

■ Calculate the percentage of haloperidol ($C_{21}H_{23}ClFNO_2$) in the portion of sample taken:

$$\text{Result} = \{(V_S - V_B) \times N \times F / W\} \times 100$$

V_S = *Titrant* volume consumed by the sample (mL)

V_B = *Titrant* volume consumed by the blank (mL)

N = actual normality of the *Titrant* (meq/mL)

F = equivalency factor, 375.86 mg/meq

W = sample weight (mg) ■^{1S} (USP36)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%

Delete the following:

- **LIMIT OF HALOPERIDOL RELATED COMPOUND A**

Standard solution: 800 µg per mL of USP Haloperidol RS and 8 µg per mL of USP Haloperidol Related Compound A RS in isopropyl alcohol containing 10 mL of dilute hydrochloric acid (1 in 100) in each 100 mL of solution.

Sample solution: Dissolve about 80 mg of Haloperidol, accurately weighed, in 80 mL of isopropyl alcohol in a 100-mL volumetric flask. Add 10 mL of dilute hydrochloric acid (1 in 100), dilute with isopropyl alcohol to volume, and mix.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV-Vis

Analytical wavelength: 335 nm

Blank: Isopropyl alcohol containing 10 mL of dilute hydrochloric acid (1 in 100) in each 100 mL of solution

Analysis

Samples: *Blank*, *Standard solution* and *Sample solution*
Determine the absorbances of the *Sample solution* and the *Standard solution* at the wavelength of maximum absorbance.

Acceptance criteria: The absorbance of the *Sample solution* is not greater than that of the *Standard solution*, corresponding to NMT 1.0%. ■^{1S} (USP36)

Add the following:

- **ORGANIC IMPURITIES**

Prepare the solutions immediately before use, and protect from light.

Solution A: 17 g/L of tetrabutylammonium hydrogen sulfate

Solution B: Acetonitrile

Mobile phase: See *Table 1*. [NOTE—The dwell volume is 1.2 mL.]

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
17	50	50
22	50	50

System suitability solution: 10 mg/mL of USP Haloperidol RS and 20 µg/mL each of USP Haloperidol Related Compound A RS and USP Haloperidol Related Compound B RS in methanol. [NOTE—Haloperidol related compound A is used for identification purposes only.]

Standard solution: 50 µg/mL of USP Haloperidol RS in methanol

Sample solution: 10 mg/mL of Haloperidol in methanol

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 3.0 between the haloperidol related compound B and haloperidol peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Haloperidol taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of an individual impurity from the *Sample solution*

r_S = peak response of haloperidol from the *Standard solution*

C_S = concentration of USP Haloperidol RS in the *Standard solution* (mg/mL)

C_U = concentration of Haloperidol in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. [NOTE—Disregard any peak with an area less than 0.05% of the main peak.]

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Haloperidol related compound B	0.9	1.4	0.3
Haloperidol	1.0	—	—
Haloperidol related compound A	1.6	1.0	0.2
Any other individual impurity	—	1.0	0.10
Total impurities	—	—	0.5

■1S (USP36)

SPECIFIC TESTS

Delete the following:

• **MELTING RANGE OR TEMPERATURE** <741>: 149°–155°, determined after drying in a vacuum at 60° for 3 h ■1S (USP36)

• **LOSS ON DRYING** <731>

Analysis: Dry a sample under vacuum at 60° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. ■Store at room temperature. ■1S (USP36)

Change to read:

• USP REFERENCE STANDARDS <11>

USP Haloperidol RS

USP Haloperidol Related Compound A RS

4,4'-Bis[4-*p*-chlorophenyl)-

4-hydroxypiperidino]butyrophenone.

C₃₂H₃₆Cl₂N₂O₃ 567.56

■USP Haloperidol Related Compound B RS

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-

1-(2-fluorophenyl)butan-1-one.

C₂₁H₂₃ClFNO₂ 375.86 ■1S (USP36)

Hypromellose

Change to read:

■Portions of this monograph that are national USP text, and are not part of the harmonized text, are marked with symbols (♦) to specify this fact. ■1S (USP36)

Cellulose, 2-hydroxypropyl methyl ether;

Cellulose hydroxypropyl methyl ether [9004-65-3].

DEFINITION

Hypromellose is a methyl and hydroxypropyl mixed ether of cellulose. It contains, calculated on the dried basis, methoxy (–OCH₃: 31.03) and hydroxypropoxy (–OC₃H₆OH: 75.09) groups conforming to the limits for the types of Hypromellose (hydroxypropyl methylcellulose) set forth in the table below.

Substitution Type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

IDENTIFICATION

• A.

Sample: 1 g

Analysis: Gently add the *Sample* to the top of 100 mL of water in a beaker, and allow to disperse over the surface, tapping the top of the container to ensure an even dispersion of the substance. Allow the beaker to stand for 1–2 min.

Acceptance criteria: The powdered material aggregates on the surface.

• B.

Sample: 1 g

Analysis: Add the *Sample* to 100 mL of boiling water, and stir the mixture using a magnetic stirrer with a bar 25 mm long.

Acceptance criteria: A slurry is formed, but the powdered material does not dissolve. Cool the slurry to 10°, and stir using a magnetic stirrer: the resulting liquid is a clear or slightly turbid solution with thickness dependent on the viscosity grade.

• C.

Solution A: Sulfuric acid and water (9:1). [NOTE—Carefully add sulfuric acid to water.]

Sample solution: 0.1 mL of the solution prepared for *Identification test B*

Analysis: To the *Sample solution*, add 9 mL of *Solution A*, and shake. Heat in a water bath for exactly 3 min, immediately cool in an ice bath, and add carefully

0.6 mL of ninhydrin TS. Shake, and allow to stand at 25°.

Acceptance criteria: A red color develops at first that changes to purple within 100 min.

• **D.**

Sample solution: 2–3 mL of the solution prepared for Identification test B

Analysis: Pour the *Sample solution* onto a glass slide as a thin film, and allow the water to evaporate.

Acceptance criteria: A coherent, clear film forms on the glass slide.

• **E.**

Sample solution: 50 mL of the solution prepared in Identification test B

Analysis: Add the *Sample solution* to exactly 50 mL of water in a beaker. Insert a thermometer into the solution. Stir the solution on a magnetic stirrer/hot plate, and begin heating at a rate of 2° to 5°/min. Determine the temperature at which a turbidity increase begins to occur, and designate this temperature as the flocculation temperature.

Acceptance criteria: The flocculation temperature is higher than 50°.

ASSAY

Change to read:

• **PROCEDURE**

[CAUTION—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the *Standard solution* and the *Sample solution* in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]

Apparatus: For the reaction vial, use a 5-mL pressure-tight serum vial, 50 mm in height, 20 mm in outside diameter, and 13 mm in inside diameter at the mouth. The vial is equipped with a pressure-tight septum having a polytetrafluoroethylene-faced butyl rubber and an airtight seal using an aluminum crimp or any sealing system that provides sufficient airtightness. Use a heater having a heating module that has a square-shape aluminum block with holes 20 mm in diameter and 32 mm in depth, into which the reaction vial fits. The heating module is also equipped with a magnetic stirrer capable of mixing the contents of the vial, or use a reciprocal shaker that performs a reciprocating motion of about 100 times/min.

Hydriodic acid: Use a reagent having a typical concentration of HI of about 57%.

Internal standard solution: 30 mg/mL of *n*-octane in *o*-xylene

Standard solution: Into a suitable serum vial, weigh between 60 and 100 mg of adipic acid, and add 2.0 mL of *Hydriodic acid* and 2.0 mL of *Internal standard solution*. Close the vial securely with a suitable septum stopper. Weigh the vial and contents, add between 15 μ L and 22 μ L of isopropyl iodide through the septum with a syringe, weigh again, and calculate the weight of isopropyl iodide added, by difference. Add 45 μ L of methyl iodide similarly, weigh again, and calculate the weight of methyl iodide added, by difference. Shake the reaction vial well, and allow the layers to separate. Use the upper layer as the *Standard solution*.

Sample solution: Transfer 0.065 g of dried Hypromellose to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum-type closure, add between 60 and 100 mg of adipic acid, and pipet 2.0 mL of *Internal standard solution* into the vial. Cautiously pipet 2.0 mL of *Hydriodic acid* into the mixture, immediately cap the vial tightly, and weigh. Using the magnetic stirrer equipped in the heating module, or using a reciprocal shaker, mix the contents of the vial continuously, heating and maintaining the temperature of the contents at

130 \pm 2° for 60 min. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial well by hand at 5-min intervals during the initial 30 min of the heating time. Allow the vial to cool, and weigh. If the weight loss is \geq 0.50% of the contents or there is evidence of a leak, discard the mixture, and prepare another *Sample solution*.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Thermal conductivity or hydrogen flame-ionization

Column: 3- to 4-mm \times 1.8- to 3-m glass; packed with 20% liquid phase G28 on 100- to 120-mesh support **■S1D■**15 (USP36) that is not silanized. [NOTE—Use a column giving well-resolved peaks of methyl iodide, isopropyl iodide, and the internal standard, in that order.]

Column temperature: 100°

Carrier gas: Use helium with the thermal conductivity detector; helium or nitrogen can be used for the hydrogen flame-ionization detector.

Flow rate: With the *Standard solution*, adjust the flow rate so that the retention time of the internal standard is about 10 min.

Injection volume: 1–2 μ L

Analysis

Samples: Upper layer of the *Standard solution* and the *Sample solution*

Calculate the percentage of methoxy (–OCH₃) in the portion of Hypromellose taken:

$$\text{Result} = 21.864 \times (R_{Ua}/R_{Sa}) \times (W_{Sa}/W_U)$$

R_{Ua} = peak area ratio of methyl iodide to *n*-octane from the *Sample solution*

R_{Sa} = peak area ratio of methyl iodide to *n*-octane from the *Standard solution*

W_{Sa} = weight of methyl iodide in the *Standard solution* (mg)

W_U = weight of Hypromellose, calculated on the dried basis, taken for the *Sample solution* (mg)

Calculate the percentage of hydroxypropoxy (–OC₃H₆OH) in the portion of Hypromellose taken:

$$\text{Result} = 44.17 \times (R_{Ub}/R_{Sb}) \times (W_{Sb}/W_U)$$

R_{Ub} = peak area ratio of isopropyl iodide to *n*-octane from the *Sample solution*

R_{Sb} = peak area ratio of isopropyl iodide to *n*-octane from the *Standard solution*

W_{Sb} = weight of isopropyl iodide in the *Standard solution* (mg)

W_U = weight of Hypromellose, calculated on the dried basis, taken for the *Sample solution* (mg)

Acceptance criteria: See the limits, calculated on the dried basis, in the table in the *Definition*.

IMPURITIES

- **RESIDUE ON IGNITION** <281>: NMT 1.5% on a 1.0-g sample
- **HEAVY METALS**, *Method III* <231>: NMT 20 ppm

SPECIFIC TESTS

- **pH** <791>: 5.0–8.0, measured on the solution prepared in the tests for *Viscosity* at a temperature of 20 \pm 2°. Read the indicated pH value after the probe has been immersed for 5 \pm 0.5 min.
- **LOSS ON DRYING** <731>
 - Analysis:** Dry 1.0 g at 105° for 1 h.
 - Acceptance criteria:** NMT 5.0%
- **VISCOSITY** <911>
 - For hypromellose samples having a viscosity type of less than 600 mPa \cdot s

Sample solution: Transfer a quantity of Hypromellose equivalent to 4 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle. Add hot water to obtain a total weight of the sample and water of 200.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10–20 min until the particles are thoroughly dispersed and wetted out. Scrape down the walls of the bottle with a spatula, if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water bath equilibrated at a temperature below 10° for another 20–40 min. Adjust the solution weight, if necessary, to 200.0 g, using cold water. Centrifuge the solution, if necessary, to expel any entrapped air. If any foam is present, remove with a spatula.

Analysis: Determine the viscosity in a suitable viscosimeter of the Ubbelohde type as directed in *Viscosity* (911).

Acceptance criteria: 80%–120% of the viscosity stated on the label

For hypromellose samples having a viscosity type of 600 mPa · s or higher

Sample solution: Transfer a quantity of Hypromellose equivalent to 10 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle, and add hot water to obtain a total weight of the sample and water of 500.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10–20 min until the particles are thoroughly dispersed and wetted out. Scrape down the walls of the bottle with a spatula, if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water bath equilibrated at a temperature below 10° for another 20–40 min. Adjust the solution weight if necessary to 500.0 g, using cold water. Centrifuge the solution, if necessary, to expel any entrapped air. If any foam is present, remove with a spatula.

Analysis: Equip a suitable single-cylinder type rotational viscosimeter (Brookfield type LV Model, or equivalent), and determine the viscosity of this solution at $20 \pm 0.1^\circ$ under the operating conditions specified in *Table 1*.

Table 1

Labeled Viscosity ^a (mPa · s)	Rotor No.	Revolution (rpm)	Calculation Multiplier
600 or more and less than 1400	3	60	20
1400 or more and less than 3500	3	12	100
3500 or more and less than 9500	4	60	100
9500 or more and less than 99,500	4	6	1000
99,500 or more	4	3	2000

^a The Labeled Viscosity is based on the manufacturer's specifications.

Allow the spindle to rotate for 2 min before taking the measurement. Allow a rest period of 2 min between subsequent measurements. Repeat the operation twice to rotate the spindle as specified above, and average the three readings.

Acceptance criteria: 75%–140% of the viscosity stated on the label

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. No storage requirements are specified.
- **LABELING:** Label it to indicate its substitution type and its nominal viscosity value in millipascals per second (mPa · s).

Add the following:

Irinotecan Hydrochloride Injection

DEFINITION

Irinotecan Hydrochloride Injection is a sterile solution of Irinotecan Hydrochloride in Water for Injection. It contains NTL 90.0% and NMT 110.0% of the labeled amount of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$).

IDENTIFICATION

• A. ULTRAVIOLET ABSORPTION (197U)

Sample solution: 4 µg/mL

Medium: Methanol

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• PROCEDURE

Buffer: Dissolve 2 g of sodium 1-hexanesulfonate and 2 mL of triethylamine in 1 L of water.

Mobile phase: Acetonitrile and *Buffer* (34:66). Adjust with phosphoric acid to a pH of 2.5.

Standard solution: 0.04 mg/mL of USP Irinotecan Hydrochloride RS in *Mobile phase*. Sonication and shaking may be used to aid dissolution.

Sample solution: 0.04 mg/mL of irinotecan hydrochloride in *Mobile phase* from Injection

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Irinotecan Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of irinotecan hydrochloride in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$), 677.18

M_{r2} = molecular weight of irinotecan hydrochloride, anhydrous ($C_{33}H_{38}N_4O_6 \cdot HCl$), 623.14

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• ORGANIC IMPURITIES

Solution A: Dissolve 2 g of sodium 1-hexanesulfonate and 1 mL of triethylamine in 1 L of water. Adjust with phosphoric acid to a pH of 2.5.

Solution B: Acetonitrile
Mobile phase: See Table 1.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
20	80	20
50	65	35
63	50	50
64	80	20
70	80	20

Diluent: Acetonitrile, phosphoric acid, and *Solution A* (500:15:500)

System suitability solution: 0.2 mg/mL of USP Irinotecan Hydrochloride RS and 0.4 µg/mL of irinotecan related compound E in *Diluent*, added stepwise, if necessary. Sonication may be used to aid dissolution.

Sample solution: 0.2 mg/mL of irinotecan hydrochloride in *Diluent* from Injection

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Temperatures

Column: 55°

Sample: 15°

Injection volume: 25 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 4.0 between irinotecan and irinotecan related compound E

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Irinotecan Hydrochloride Injection taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak area of each impurity from the *Sample solution*

r_T = sum of the peak areas from the *Sample solution*

F = relative response factor for each individual impurity (see Table 2)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Irinotecan related compound B ^a	0.53	0.74	0.2
Camptothecin ^b	0.65	—	—
Irinotecan	1.00	—	—
7-Ethyl-camptothecin ^c	1.16	—	—

^a (S)-4,11-Diethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione.

^b (S)-4-Ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione. It is a process impurity and is controlled in the API monograph.

^c Irinotecan related compound E. It is a process impurity and is controlled in the API monograph.

Table 2 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any unspecified impurity	—	1.0	0.2
Total impurities	—	—	1.0

^a (S)-4,11-Diethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione.

^b (S)-4-Ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione. It is a process impurity and is controlled in the API monograph.

^c Irinotecan related compound E. It is a process impurity and is controlled in the API monograph.

SPECIFIC TESTS

• **BACTERIAL ENDOTOXINS** <85>: NMT 0.83 USP Endotoxin Units/mg of irinotecan hydrochloride

• **STERILITY TESTS** <71>: Meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*

• **pH** <791>: 3.0–3.8

• **PARTICULATE MATTER** <788>: Meets the requirements for small-volume injections

• **OTHER REQUIREMENTS:** Meets the requirements under *Injections* <1>

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in single-dose vials, protected from light. Store at controlled room temperature.

• **LABELING:** Label it to indicate that it is to be diluted with either 5% dextrose solution (USP) or 0.9% Sodium Chloride Injection (USP) prior to intravenous infusion.

• **USP REFERENCE STANDARDS** <11>

USP Irinotecan Hydrochloride RS

USP Irinotecan Related Compound E RS

(S)-4,11-Diethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione.

C₂₂H₂₀N₂O₄ 376.41

USP Endotoxin RS_{US} (USP36)

Isosorbide Mononitrate Extended-Release Tablets

DEFINITION

Isosorbide Mononitrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of isosorbide mononitrate (C₆H₉NO₆).

IDENTIFICATION

• **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** <201>

Standard solution: 0.5 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in absolute alcohol

Sample stock solution: To a portion of the powder from NLT 20 Tablets in a suitable container, nominally equivalent to 120 mg of isosorbide mononitrate, add 50.0 mL of absolute alcohol, sonicate for 10 min, and centrifuge.

Sample solution: Transfer 10 mL of supernatant from the *Sample stock solution* to a 50-mL volumetric flask, and dilute with absolute alcohol to volume.

Spray reagent: Dissolve 1 g of soluble starch in 100 mL of boiling water. Cool, and add 0.5 g of potassium iodide.

Application volume: 20 µL

Developing solvent system: Chloroform and methanol (95:5)

Analysis**Samples:** *Standard solution* and *Sample solution*Examine the plate under short-wavelength UV light, marking any observed spots. Visualize nitrates on the plate by spraying with *Spray reagent* and illuminating with short-wavelength UV light for 10 min.**Acceptance criteria:** Isosorbide mononitrate and other nitrates appear as a violet spot on a white-to-light violet background.

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY• **PROCEDURE****Mobile phase:** Methanol and water (200:800)**Standard solution A:** 0.15 mg/mL of isosorbide mononitrate related compound A from USP Diluted Isosorbide Mononitrate Related Compound A RS in water**Standard solution B:** Equivalent to 0.12 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS prepared as follows. Dissolve the sample in water, add methanol equivalent to 20% of the flask volume, and then dilute with water to volume.**System suitability solution:** Equivalent to 0.12 mg/mL of isosorbide mononitrate and 6 µg/mL of isosorbide mononitrate related compound A prepared as follows. Dissolve a suitable quantity of USP Diluted Isosorbide Mononitrate RS in water in a suitable volumetric flask, add a suitable amount of *Standard solution A* and methanol equivalent to 20% of the flask volume, and dilute with water to volume.**Sample solution:** 0.12 mg/mL of isosorbide mononitrate from NLT 20 Tablets finely powdered, prepared as follows. Transfer a portion of the powder, nominally equivalent to 60 mg of isosorbide mononitrate, to a 100-mL volumetric flask. Add 50 mL of methanol, and sonicate for about 30 min with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 min. Dilute the supernatant with water, and filter a portion of this solution through a suitable filter of 0.45-µm pore size.**Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 220 nm**Column:** 4-mm × 12.5-cm; packing L1**Flow rate:** 1.5 mL/min**Injection volume:** 20 µL**System suitability****Samples:** *System suitability solution* and *Standard solution B***Suitability requirements****Resolution:** NLT 1.5 between isosorbide mononitrate related compound A and isosorbide mononitrate, *System suitability solution***Tailing factor:** NMT 1.5, *Standard solution B***Relative standard deviation:** NMT 1.5%, *Standard solution B***Analysis****Samples:** *Standard solution B* and *Sample solution*Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response of isosorbide mononitrate from the *Sample solution* r_S = peak response of isosorbide mononitrate from *Standard solution B* C_S = concentration of isosorbide mononitrate in *Standard solution B* (mg/mL) C_U = nominal concentration of isosorbidemononitrate in the *Sample solution* (mg/mL)**Acceptance criteria:** 90.0%–110.0%**PERFORMANCE TESTS****Change to read:**• **DISSOLUTION** <711>**Test 1****Medium:** Water; 900 mL**Apparatus 2:** 50 rpm

The Tablets are placed in a metal helix prepared by winding 10 in of an 0.8-mm stainless steel wire around a 9/32-in shaft and pulling the coils to form a helix 1 in long.

Times: 1, 2, 4, 8, and 12 h**Mobile phase:** Methanol and water (300:700)**Standard solution:** L/1000 of USP Diluted Isosorbide Mononitrate RS in *Medium* where L is the label claim in mg/Tablet**Sample solution:** Use portions of the solution under test passed through a suitable nylon filter of 0.45-µm pore size, discarding the first 4–6 mL of the filtrate.**Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 220 nm**Column:** 4.6-mm × 25-cm; packing L1**Flow rate:** 1 mL/min**Injection volume:** 25 µL**System suitability****Sample:** *Standard solution***Suitability requirements****Relative standard deviation:** NMT 1.5%**Analysis****Samples:** *Standard solution* and *Sample solution*

Determine the amount, in mg, of isosorbide mononitrate dissolved at each interval:

$$\text{Result} = (r_U/r_S) \times C_S \times V$$

 r_U = peak response of isosorbide mononitrate from the *Sample solution* r_S = peak response of isosorbide mononitrate from the *Standard solution* C_S = concentration of isosorbide mononitrate in the *Standard solution* (mg/mL) V = volume of the *Medium* in the vessel at each time point (mL)

Calculate the amount, in mg, of isosorbide mononitrate removed by sampling at the previous time points:

$$\text{Result} = \Sigma AD \times (V_S/V)$$

 AD = amount of isosorbide mononitrate dissolved at each time point (mg) V_S = volume of the sample taken (mL) V = volume of the *Medium* in the vessel at each time point (mL)Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point:

$$\text{Result} = (AD + AR) \times (100/L)$$

 AD = amount of isosorbide mononitrate dissolved at each time point (mg) AR = amount of isosorbide mononitrate removed at the previous time point (mg) L = label claim (mg/Tablet)

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved (%)
1	15–35
2	28–48
4	43–68
8	65–90
12	NLT 80

The percentages of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* <711>.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Simulated gastric fluid (without enzymes); 500 mL

Apparatus 2: 50 rpm

Times: 1, 2, 6, and 12 h

Mobile phase: Methanol and water (400:600)

Standard stock solution: 1.2 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS diluted in *Medium*

Standard solution: 60 µg/mL of isosorbide mononitrate in *Medium* for Tablets labeled to contain 30 mg, and 120 µg/mL of isosorbide mononitrate in *Medium* for Tablets labeled to contain 60 mg, from the *Standard stock solution*

Sample solution: Pass portions of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 10-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i), in mg/mL, of isosorbide mononitrate removed at each time point:

$$\text{Result} = (r_{U(i)} / r_s) \times C_s$$

$r_{U(i)}$ = peak response of isosorbide mononitrate from the *Sample solution* at time point i

r_s = peak response of isosorbide mononitrate from the *Standard solution*

C_s = concentration of isosorbide mononitrate in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point i :

$$\text{Result} = \{C_i \times [V_0 - ((i-1)V_i)] + (\sum_{j=1}^{i-1} C_j V_j)\} \times (100/L)$$

C_i = concentration of isosorbide mononitrate at time point i (mg/mL)

V_0 = initial volume of *Medium* (mL)

V_i = volume of sample removed at each sampling time (mL)

C_j = concentration of isosorbide mononitrate at time j (mg/mL)

L = label claim (mg/Tablet)

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
1	25–45
2	35–60
6	65 • (RB 1-Aug-2012)–90
12	NLT 80

The percentages of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* <711>.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Medium: Simulated gastric fluid (without enzymes); 500 mL

Apparatus 2: 50 rpm

Time: 1, 2, 6, and 12 h

Buffer: Transfer 15.4 g of ammonium acetate and 11.5 mL of acetic acid to a 1-L volumetric flask containing 500 mL of water. Adjust with acetic acid to a pH of 4.7, and dilute with water to volume.

Mobile phase: Methanol, *Buffer*, and water (300:100:600)

Standard stock solution: 0.12 mg/mL of isosorbide mononitrate from USP Diluted Isosorbide Mononitrate RS in *Medium*

Standard solution: For Tablets labeled to contain 60 mg, use the *Standard stock solution* with no further dilution (0.12 mg/mL). For Tablets labeled to contain 30 mg, prepare 0.06 mg/mL of isosorbide mononitrate in *Medium* from the *Standard stock solution*.

Sample solutions: Pass portions of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5 µm, packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i), in mg/mL, of isosorbide mononitrate at each time point i :

$$\text{Result} = (r_{U(i)} / r_s) \times C_s$$

$r_{U(i)}$ = peak response of isosorbide mononitrate from the *Sample solution* at time point i

r_s = peak response of isosorbide mononitrate from the *Standard solution*

C_s = concentration of isosorbide mononitrate in the *Standard solution* (mg/mL)

Calculate the percentage of the label claim of isosorbide mononitrate ($C_6H_9NO_6$) dissolved at each time point i :

$$\text{Result} = \{C_i \times [V_0 - ((i-1)V_i)] + (\sum_{j=1}^{i-1} C_j V_j)\} \times (100/L)$$

C_i = concentration of isosorbide mononitrate at time point i (mg/mL)

V_0 = initial volume of *Medium* (mL)

V_i = volume of sample removed at each sampling time (mL)

C_j = concentration of isosorbide mononitrate at time j (mg/mL)

L = label claim (mg/Tablet)

Tolerances: See Table 3.

Table 3

Time (h)	Amount Dissolved (%)
1	20–40
2	30–50
6	70–90
12	NLT 85

The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Acceptance Table 2 in Dissolution* <711>.

- **UNIFORMITY OF DOSAGE UNITS** <905>: Meet the requirements
Procedure for content uniformity: Proceed as directed in the *Assay*, except use 1 Tablet instead of the portion of powdered Tablets used in the *Sample solution* in the *Assay*.

IMPURITIES

• ORGANIC IMPURITIES, PROCEDURE 1

Standard solution A: 0.0125 mg/mL of USP Isosorbide RS in acetonitrile

Standard solution B: 0.025 mg/mL of USP Isosorbide RS in acetonitrile

Standard solution C: 0.05 mg/mL of USP Isosorbide RS in acetonitrile

Sample solution: Equivalent to 5 mg/mL of isosorbide mononitrate from a portion of powdered Tablets (NLT 20) in acetonitrile. Sonicate for 10 min, and then centrifuge. Use the supernatant.

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 20 µL

Developing solvent system: Toluene, ethyl acetate, and isopropyl alcohol (53:32:15)

Detection solution: Dissolve 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 min.

Analysis

Samples: *Standard solutions* and *Sample solution*

Proceed as directed for the chapter. After developing, dry the plate with warm air for about 10 min, dip the plate in the *Detection solution*, and heat at 105° for 5 min.

Acceptance criteria: Any spot from the *Sample solution* and corresponding to the R_f value of the spots from the *Standard solutions* is not more intense than the spot from *Standard solution C*; NMT 1% of any individual impurity is found.

If the spot from the *Sample solution* is nearly as intense as the spot from *Standard solution C*, further dilute the *Sample solution* with acetonitrile (1:1), repeat the test, and compare the intensity of the isosorbide spot in the diluted *Sample solution* with the intensity of the spots from the *Standard solutions*, correcting the percentage level for the additional dilution of the *Sample solution*.

[NOTE—The R_f values of isosorbide and isosorbide mononitrate are about 0.2 and 0.6, respectively.]

• ORGANIC IMPURITIES, PROCEDURE 2

Mobile phase: Methanol and water (250:750)

Isosorbide mononitrate related compound A stock solution: 0.3 mg/mL of isosorbide mononitrate related compound A from USP Diluted Isosorbide Mononitrate Related Compound A RS in water

Isosorbide dinitrate stock solution: 0.15 mg/mL of isosorbide dinitrate from USP Diluted Isosorbide Dinitrate RS in methanol

Standard stock solution: 6.0 µg/mL each of isosorbide mononitrate related compound A and isosorbide dinitrate from *Isosorbide mononitrate related compound A stock solution* and *Isosorbide dinitrate stock solution*, respectively, diluted with water

System suitability solution: Transfer a quantity of USP Diluted Isosorbide Mononitrate RS, equivalent to 24 mg of isosorbide mononitrate, to a 100-mL volumetric flask. Add 10.0 mL of *Standard stock solution* and 20 mL of methanol, and dilute with water to volume.

Standard solution: Transfer 10.0 mL of *Standard stock solution* and 20 mL of methanol to a 100-mL volumetric flask. Dilute with water to volume.

Sample stock solution: Transfer a portion of the powder from NLT 20 Tablets, equivalent to 60 mg of isosorbide mononitrate, to a 50-mL volumetric flask. Add 40 mL of methanol, and sonicate for about 30 min with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 min. Dilute 10 mL of the supernatant with water to 50 mL. Pass a portion of this solution through a suitable filter of 0.45-µm pore size, and use the filtrate.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for isosorbide mononitrate related compound A, isosorbide mononitrate, and isosorbide dinitrate are about 0.9, 1.0, and 5.6, respectively.]

Suitability requirements

Resolution: NLT 1.0 between isosorbide mononitrate related compound A and isosorbide mononitrate, *System suitability solution*

Relative standard deviation: NMT 10% for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of isosorbide mononitrate related compound A and isosorbide dinitrate in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of isosorbide mononitrate related compound A or isosorbide dinitrate from the *Sample solution*

r_S = peak area of isosorbide mononitrate related compound A or isosorbide dinitrate from the *Standard solution*

C_S = concentration of USP Diluted Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of isosorbide mononitrate in the *Sample solution* (mg/mL)

Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak area for each impurity from the *Sample solution*

r_T = sum of the areas of all the peaks from the *Sample solution*

Acceptance criteria

Individual impurities: NMT 0.25% each of isosorbide mononitrate related compound A and isosorbide dinitrate

Total other impurities: NMT 0.25%

Total impurities: NMT 0.5% including isosorbide mononitrate related compound A and isosorbide dinitrate

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature of 20°–30°.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** <11>
USP Isosorbide RS
[NOTE—The following Reference Standards are dry mixtures of an active component and suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component based on the content stated on the label.]
USP Diluted Isosorbide Dinitrate RS
USP Diluted Isosorbide Mononitrate RS
USP Diluted Isosorbide Mononitrate Related Compound A RS
1,4:3,6-Dianhydro-D-glucitol 2-nitrate.
 $C_6H_9NO_6$ 191.14

Isotretinoin Capsules**DEFINITION**

Isotretinoin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$).

[**CAUTION**—Isotretinoin is teratogenic. Avoid inhalation and skin contact.]

Avoid exposure to strong light, and use low-actinic glassware in the performance of the following procedures.

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**PROCEDURE**

Protect the *System suitability solution*, *Standard solution*, *Sample stock solution*, and *Sample solution* from direct light.

Diluent: Heat 0.1 N sodium hydroxide to about 60°–70°. Cool to room temperature, purge with helium or nitrogen, and store in a plastic container.

Solution A: 0.5% acetic acid in methanol

Solution B: 0.5% acetic acid in water

Mobile phase: *Solution A* and *Solution B* (71:29)

System suitability solution: 0.04 mg/mL of USP Isotretinoin RS and 0.02 mg/mL of USP Tretinoin RS in *Diluent*

Standard solution: 0.04 mg/mL of USP Isotretinoin RS in *Diluent*

Sample stock solution: 0.4 mg/mL of isotretinoin in *Diluent* prepared as follows. Transfer NLT 10 Capsules to a suitable volumetric flask. Add *Diluent* to the volumetric flask to fill about 50% of the volume, sonicate for 1 h with occasional shaking to disperse all of the contents, and dilute with *Diluent* to volume.

Sample solution: 0.04 mg/mL of isotretinoin in *Diluent* from the *Sample stock solution*. Pass the solution

through a suitable membrane filter of 0.45- μ m or finer pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 353 nm

Column: 4.6-mm \times 25-cm; packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for isotretinoin and tretinoin are 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 2.0 between the isotretinoin and tretinoin peaks, *System suitability solution*

Column efficiency: NLT 2000 for the isotretinoin peak, *System suitability solution*

Tailing factor: NMT 2.0 for the isotretinoin peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of isotretinoin in the *Standard solution* (mg/mL)

C_U = nominal concentration of isotretinoin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS**Change to read:****DISSOLUTION** <711>

[**CAUTION**—Carry out all the tests under subdued light and use low-actinic glassware.]

Test 1**Medium**

Stage 1: Simulated gastric fluid with pepsin, prepared freshly and purged with nitrogen

Stage 2: 0.13 N sodium hydroxide (5 g/L of sodium hydroxide in water). Prepare fresh, and purge with nitrogen.

Apparatus (see *Disintegration* <701>): No disks; the apparatus is adjusted so that the bottom of the basket-rack assembly descends to 1.0 ± 0.1 cm from the inside bottom surface of the vessel on the downward stroke; the 10-mesh stainless steel cloth in the basket-rack assembly is replaced with a 40-mesh stainless steel cloth; a 10-mesh stainless-steel cloth is fitted to the top of the basket-rack assembly.

Time: 60 min

Standard solution: Transfer 10 mg of USP Isotretinoin RS to a 200-mL volumetric flask. Add 25.0 mL of *Stage 1 Medium* and about 150 mL of *Stage 2 Medium*, sonicate until completely dissolved (about 20 min), and dilute with *Stage 2 Medium* to volume. Pass 20 mL of this solution through a suitable filter, discarding the first 5 mL. Dilute 5.0 mL of the filtrate with *Stage 2 Medium* to 50 mL.

Sample solutions: Perform a dissolution test on each of 6 Capsules: place 1 Capsule in one of the tubes in each of six basket-rack assemblies. Place each basket in a 1-L beaker containing 100 mL of *Stage 1 Medium* in a bath having a temperature of $37.0 \pm 0.5^\circ$. Allow to stand for 30 min. Carefully add 800 mL of *Stage 2 Medium* to each beaker. With the disintegration apparatus operating, connect each basket-rack assembly to the drive rod in a timed sequence. After 60 min, withdraw 20 mL of *Medium* (*Stage 1* and *Stage 2*), immediately pass the solution through a suitable membrane filter of 0.45- μ m pore size, discard the first 5 mL, and collect the solution in argon-charged glassware. Dilute, if necessary, with *Stage 2 Medium* to obtain a theoretical concentration of 5.5 μ g/mL of isotretinoin, assuming complete dissolution, based on the label claim.

Capsule shell correction solution: Empty the contents of 3 Capsules. Wash the Capsule shells in several 20-mL aliquots of chloroform. Allow the Capsule shells to air dry. Place the Capsule shells in a 1-L flask containing 100 mL of *Stage 1 Medium* and 800 mL of *Stage 2 Medium*. Allow the flask to stand for about 1 h in a bath having a temperature of $37.0 \pm 0.5^\circ$, stirring occasionally. Filter, and dilute as described for the *Sample solution*.

Analysis

Detector: UV 343 nm

Blank: *Medium* (*Stage 1* and *Stage 2*)

Samples: *Standard solution*, *Sample solutions*, and *Capsule shell correction solution*

Determine the amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved, correcting for the Capsule shell absorbance. Calculate the percentage of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved:

$$\text{Result} = [(A_U - A_C)/A_S] \times (C_S/L) \times D \times 100$$

A_U = absorbance of the *Sample solution*

A_C = absorbance of the *Capsule shell correction solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Isotretinoin RS in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

D = dilution factor for the *Sample solution*

Tolerances: NLT 80% (Q) of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: 0.05 M phosphate buffer, pH 7.8, containing 0.5% (w/v) solid *N,N*-dimethyldodecylamine *N*-oxide; 900 mL

Apparatus 1: 20-mesh basket; 100 rpm

Time: 90 min

Buffer solution: 3.4 mg/mL of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 2.10 ± 0.05 .

Mobile phase: Methanol and *Buffer solution* (81:19)

Standard solution: Transfer about 44 mg of USP Isotretinoin RS to a 100-mL volumetric flask. Add 15 mL of 1-propanol, and sonicate for about 15 min. Add 50 mL of *Medium*, and sonicate for 10 min. Dilute with *Medium* to volume. Transfer 5.0 mL to a 100-mL volumetric flask, and dilute with *Medium* to volume. Dilute this solution with *Medium* to obtain a final concentration of about ($L/1000$) mg/mL, where L is the label claim, in mg/Capsule.

Sample solution: Pass a portion of the solution under test through a suitable membrane filter of 0.45- μ m pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 358 nm

Column: 4.6-mm \times 5-cm; 5- μ m packing L1

Flow rate: 2.0 mL/min

Injection volume: 10 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Medium: Borate buffer, pH 8.0, containing 0.5% cetrimide and 50 mg/L of pancreatin. Dissolve 12.37 g of boric acid and 14.91 g of potassium chloride in water, and dilute with water to 1 L. To 250 mL of this solution add 19.5 mL of 0.2 M sodium hydroxide solution, and dilute with water to 1 L. Adjust with 0.2 M sodium hydroxide to a pH of 8.00 ± 0.05 , if necessary. Add 5 g of cetrimide. Just before starting the test, dissolve a quantity of pancreatin to obtain a final concentration of 50 mg/L; 900 mL.

Apparatus 2: 75 rpm, with sinkers

Time: 90 min

Standard solution: 0.45 mg/mL of USP Isotretinoin RS in 0.1 N sodium hydroxide. Dilute this solution with *Medium* to obtain a final concentration of ($L/1000$) mg/mL, where L is the label claim in mg/Capsule.

Sample solution: Pass a portion of the solution under test through a suitable membrane filter of 0.45- μ m pore size.

Mobile phase: 0.5% acetic acid in methanol and 0.5% acetic acid in water (71:29)

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 353 nm

Column: 4.6-mm \times 25-cm; 10- μ m packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1800 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_s = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 70% (Q) of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) is dissolved.

• **Test 4:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.

Medium: 50 mM monobasic potassium phosphate at pH 7.4 containing 70 mg/L of pancreatin and 4.5% (v/v) of Milloxid L (lauryl dimethyl amine oxide) prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 920 mL of water. Adjust by the addition of approximately 35 mL of 1 N sodium hydroxide to a pH of 7.4 ± 0.1 . Add 70 mg of pancreatin and 45 mL of lauryl dimethyl amine oxide, and stir gently to mix. The pancreatin should be added on the day of use; 900 mL. [NOTE—Not all of the pancreatin visibly dissolves.]

Apparatus 2: 75 rpm, with spiral coated sinker. [NOTE—A suitable sinker is available as catalog number CAPWHT-02 from www.qia-llc.com.]

Time: 90 min

Standard stock solution 1: 0.28 mg/mL of USP Isotretinoin RS prepared as follows. Transfer USP Isotretinoin RS to a suitable volumetric flask, and add methanol equivalent to 10% of the final volume. Sonicate to dissolve, and dilute with *Medium* to volume.

Standard solution: 0.028 mg/mL of USP Isotretinoin RS in *Medium*, from *Standard stock solution 1*

Standard stock solution 2: 8.8 µg/mL of USP Tretinoin RS prepared as follows. Transfer USP Tretinoin RS to a suitable volumetric flask, and add methanol equivalent to 20% of the final volume. Sonicate to dissolve, and dilute with *Medium* to volume to obtain a 0.22-mg/mL solution. Transfer 2 mL of this solution to a 50-mL volumetric flask, and dilute with *Medium* to volume.

System suitability solution: 45 µg/mL of USP Isotretinoin RS and 0.88 µg/mL of USP Tretinoin RS in *Medium* from *Standard stock solution 1* and *Standard stock solution 2*

Sample solution: Pass a portion of the solution under test through a suitable PVDF membrane filter of 0.45-µm pore size.

Mobile phase: Methanol, water, and glacial acetic acid (80: 20: 0.5)

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: 353 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Temperatures

Column: 40°

Autosampler: 4°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times of isotretinoin and tretinoin are 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 3.0 between the isotretinoin and tretinoin peaks, *System suitability solution*

Tailing factor: 0.8–1.3 for the isotretinoin peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Calculate the percentage of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) dissolved:

$$\text{Result} = (r_u/r_s) \times (C_s/L) \times V \times 100$$

r_u = peak response from the *Sample solution*

r_s = peak response from the *Standard solution*

C_s = concentration of USP Isotretinoin RS in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 75% (Q) of the labeled amount of isotretinoin ($C_{20}H_{28}O_2$) is dissolved. (RB 1-Oct-2012)

• **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

• ORGANIC IMPURITIES

Methylene chloride reagent: Transfer 50 g of sodium bicarbonate to 1000 mL of methylene chloride, shake, and allow to stand overnight. At the time of use, filter suitable portions of this solution, and add 10 mg of butylated hydroxytoluene per mL of solution.

Mobile phase: Hexanes, ethyl acetate, and glacial acetic acid (970: 30: 0.1)

System suitability stock solution: 1 mg/mL each of USP Isotretinoin RS and USP Tretinoin RS in *Methylene chloride reagent*

System suitability solution: 0.01 mg/mL each of USP Isotretinoin RS and USP Tretinoin RS in hexanes from *System suitability stock solution*

Standard stock solution: 0.5 mg/mL of USP Tretinoin RS in *Methylene chloride reagent*

Standard solution: 1.0 µg/mL of USP Tretinoin RS from the *Standard stock solution* in hexanes

Sample stock solution: Take a number of Capsules equivalent to about 200 mg of isotretinoin, and with a sharp blade carefully open the Capsules without loss of material. Transfer the contents by pipetting 5 mL of *Methylene chloride reagent* over each Capsule, and rinsing with hexanes. Collect the washings in a 500-mL volumetric flask, dilute with hexanes to volume, and mix.

Sample solution: 0.1 mg/mL of isotretinoin in hexanes. Transfer 50.0 mL of *Sample stock solution* to a 200-mL volumetric flask, and dilute with hexanes to volume.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 365 nm

Column: 4.6-mm × 25-cm; packing L3

Flow rate: 1 mL/min

Injection volume: 20 µL in *System suitability* and 50 µL in *Analysis*

Run time: NLT 2 times the retention time of isotretinoin

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for isotretinoin and tretinoin are about 0.75 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between isotretinoin and tretinoin

Tailing factor: NMT 2.5 for the isotretinoin peak

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*
Record the chromatograms, and measure the peak responses.

Acceptance criteria: The peak response for any impurity is NMT that of the tretinoin response from the *Standard solution* (1.0%); and the sum of all the peak responses, excluding that of isotretinoin, from the *Sample solution*, is NMT 1.5 times the tretinoin response from the *Standard solution* (1.5%).

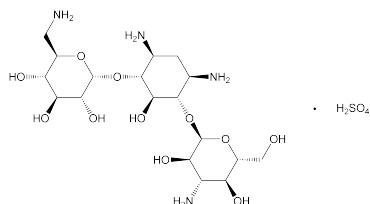
ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light. Store at controlled room temperature in a dry place.

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** (11)
USP Isotretinoin RS
USP Tretinoin RS

Kanamycin Sulfate

Change to read:



$C_{18}H_{36}N_4O_{11} \cdot H_2SO_4$ 582.58
D-Streptamine, O-3-amino-3-deoxy- α -D-glucopyranosyl(1 \rightarrow 6)-O-[6-amino-6-deoxy- α -D-glucopyranosyl(1 \rightarrow 4)]-2-deoxy-, sulfate (1:1) (salt);
Kanamycin sulfate (1:1) (salt) \blacksquare 1S (USP36) [25389-94-0].

DEFINITION

Kanamycin Sulfate has a potency equivalent to NLT 750 μ g/mg of kanamycin ($C_{18}H_{36}N_4O_{11}$), calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A. \blacksquare INFRARED ABSORPTION** (197K) \blacksquare 1S (USP36)
- **B. IDENTIFICATION TESTS—GENERAL, Sulfate** (191): Meets the requirements
- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**
Mobile phase: 0.115 N sodium hydroxide solution
System suitability solution: 20 μ g/mL of USP Amikacin RS and 8 μ g/mL of USP Kanamycin Sulfate RS in water
Standard solution: 8 μ g/mL of USP Kanamycin Sulfate RS in water
Sample solution: 8 μ g/mL of Kanamycin Sulfate in water
Chromatographic system
(See *Chromatography* (621), *System Suitability*.)
Mode: LC
Detector: Pulsed amperometric electrochemical detector
Working electrode: Gold
Reference electrode: pH silver–silver chloride \blacksquare 1S (USP36)

Waveform: See *Table 1*.

Table 1

Time (s)	Potential (V)	Integration
0.00	+0.04	—
0.30	+0.04	Begin
0.50	+0.04	End
0.51	+0.80	—
0.70	+0.80	—
0.71	−0.80	—
0.90	−0.80	—

Columns

Guard: \blacksquare 4-mm \times 50-mm; 7.5- μ m \blacksquare 1S (USP36) packing L47

Analytical: 4-mm \times 25-cm; \blacksquare 7.5- μ m \blacksquare 1S (USP36) packing L47

Flow rate: 0.5 mL/min

Injection volume: 20 μ L

System suitability

[NOTE—The relative retention times for kanamycin and amikacin are about 1.0 and 1.3, respectively.]

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 3 between kanamycin and amikacin, *System suitability solution*

Tailing factor: NMT 2, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in μ g/mg, of kanamycin ($C_{18}H_{36}N_4O_{11}$) in the portion of Kanamycin Sulfate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Kanamycin Sulfate RS in the *Standard solution* (μ g/mL)

C_U = concentration of Kanamycin Sulfate in the *Sample solution* (μ g/mL)

P = potency of kanamycin in USP Kanamycin Sulfate RS (μ g/mg)

Acceptance criteria: NLT 750 μ g/mg on the dried basis

IMPURITIES

• RESIDUE ON IGNITION (281)

Analysis: Moisten the charred residue with 2 mL of nitric acid and 5 drops of sulfuric acid.

Acceptance criteria: NMT 1.0%

• ORGANIC IMPURITIES

Adsorbent: 0.25-mm layer of chromatographic silica gel

Developing solvent system: 75 mg/mL of monobasic potassium phosphate in water

Spray reagent: 10 mg/mL of ninhydrin in butyl alcohol

Standard solution 1: 30 mg/mL of USP Kanamycin Sulfate RS in water

Standard solution 2: 0.90 mg/mL of USP Kanamycin Sulfate RS in water

Sample solution: 30 mg/mL of Kanamycin Sulfate in water

Application volume: 1 μ L

Analysis: Heat the plate at 110° for 1 h immediately before use, and allow it to cool. Equilibrate for 90 min with the *Developing solvent system*.

Apply all three solutions to the plate separately, allow the spots to dry, and develop the chromatogram with the *Developing solvent system* until the solvent front

has moved three-fourths of the length of the plate. Remove the plate from the chamber, and air-dry. Spray the plate with *Spray reagent*. Dry the plate at 110° for 10 min, and examine the chromatograms.

Acceptance criteria: The chromatograms show principal spots at the same R_f value, and no secondary spot, if present from the *Sample solution*, is more intense than the principal spot of *Standard solution 2*.

SPECIFIC TESTS

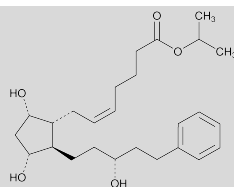
- **CRYSTALLINITY** (695): Meets the requirements
- **pH** (791)
Sample solution: 10 mg/mL
Acceptance criteria: 6.5–8.5
- **LOSS ON DRYING** (731)
Analysis: Dry 100 mg in a vacuum in a capillary-stoppered bottle at a pressure not exceeding 5 mm of mercury at 60° for 3 h.
Acceptance criteria: NMT 4.0%
- **STERILITY TESTS** (71): Where the label states that Kanamycin Sulfate is sterile, it meets the requirements when tested as directed for membrane filtration in *Test for Sterility of the Product to Be Examined*.
- **BACTERIAL ENDOTOXINS TEST** (85): Where the label states that Kanamycin Sulfate must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.67 USP Endotoxin Unit/mg of Kanamycin.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.
- **USP REFERENCE STANDARDS** (11)
 USP Amikacin RS
 USP Endotoxin RS
 USP Kanamycin Sulfate RS

Add the following:

•Latanoprost



$C_{26}H_{40}O_5$ 432.59
 5-Heptenoic acid, 7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-1-methylethyl ester, [1*R*-[1 α (*Z*),2 β (*R**),3 α ,5 α]]-;
 Isopropyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate.
 [130209-82-4].

DEFINITION

Latanoprost contains NLT 94.0% and NMT 102.0% of latanoprost ($C_{26}H_{40}O_5$), calculated on the anhydrous and solvent-free basis.

CAUTION—Wear protective glasses and gloves while handling the material. Avoid contact during pregnancy or while nursing.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197F)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• PROCEDURE

Mobile phase: Chromatographic solvent hexane and dehydrated alcohol (94:6)

System suitability solution: 2.0 mg/mL of USP Latanoprost RS and 20 μ g/mL of USP Latanoprost Related Compound A RS prepared as follows. Transfer USP Latanoprost RS and USP Latanoprost Related Compound A RS into a suitable volumetric flask, dissolve in dehydrated alcohol equivalent to 20% of the final volume, and dilute with hexane to volume.

Standard solution: 2.0 mg/mL of USP Latanoprost RS prepared as follows. Transfer USP Latanoprost RS into a suitable volumetric flask, dissolve in dehydrated alcohol equivalent to 20% of the final volume, and dilute with hexane to volume.

Sample solution: 2.0 mg/mL of Latanoprost prepared as follows. Transfer Latanoprost into a suitable volumetric flask, dissolve in dehydrated alcohol equivalent to 20% of the final volume, and dilute with hexane to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.0-mm \times 25-cm; 5- μ m packing L3

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 μ L

System suitability

Samples: *System Suitability Solution* and *Standard solution*

[NOTE—The relative retention times for latanoprost and latanoprost related compound A are 1.0 and 1.1, respectively.]

Suitability requirements

Resolution: NLT 2.0 between latanoprost and latanoprost related compound A, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of latanoprost ($C_{26}H_{40}O_5$) in the portion of Latanoprost taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Latanoprost RS in the *Standard solution* (mg/mL)

C_U = concentration of Latanoprost in the *Sample solution* (mg/mL)

Acceptance criteria: 94.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.50%

• ORGANIC IMPURITIES

Mobile phase, System suitability solution, Sample solution, and Chromatographic system: Proceed as directed in the *Assay*.

Standard solution: 0.04 mg/mL of USP Latanoprost RS in a mixture of hexane and dehydrated alcohol (80:20) prepared as follows. Transfer USP Latanoprost RS into a suitable volumetric flask, dissolve in dehydrated alcohol equivalent to 20% of the final volume, and dilute with hexane to volume.

System suitability**Samples:** *System suitability solution* and *Standard solution***Suitability requirements****Resolution:** NLT 2.0 between latanoprost and latanoprost related compound A, *System suitability solution***Relative standard deviation:** NMT 5.0%, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Latanoprost taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

 r_U = peak area of each impurity from the *Sample solution* r_S = peak area of latanoprost from the *Standard solution* C_S = concentration of latanoprost in the *Standard solution* (mg/mL) C_U = concentration of Latanoprost in the *Sample solution* (mg/mL) F = relative response factor for each individual impurity (see *Table 1*)**Acceptance criteria:** See *Table 1*. Disregard any impurity peak less than 0.05%.**Table 1**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Isopropyl diphenylphosphorylpentanoate ^a	0.79	2.4	0.1
Latanoprost related compound B ^b	0.89	1.0	0.5
Latanoprost	1.00	—	—
Latanoprost related compound A ^c	1.10	1.0	3.5
Any unspecified impurity	—	1.0	0.1
Total impurities ^d	—	—	0.5

^a Isopropyl 5-(diphenylphosphoryl)pentanoate.^b Isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3S)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate.^c Isopropyl (E)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate.^d Latanoprost related compound A and Latanoprost related compound B are excluded.**• LIMIT OF LATANOPROST RELATED COMPOUND E****Solution A:** Acetonitrile, phosphoric acid, and water (300:1:700)**Solution B:** Acetonitrile, phosphoric acid, and water (800:1:200)**Mobile phase:** See *Table 2*.**Table 2**

Time (min)	Solution A (%)	Solution B (%)
0	100	0
9	100	0
10	0	100
15	0	100
16	100	0
21	100	0

Diluent: Acetonitrile and water (30:70)**Standard solution:** 1.0 µg/mL of USP Latanoprost Related Compound E RS in *Diluent***Sample solution:** 1.0 mg/mL of Latanoprost in *Diluent***Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 200 nm**Column:** 4.0-mm × 15-cm column; 5-µm packing L1**Column temperature:** 60°**Flow rate:** 1.0 mL/min**Injection volume:** 50 µL**System suitability****Sample:** *Standard solution***Suitability requirements****Relative standard deviation:** NMT 5.0%**Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of latanoprost related compound E in the portion of Latanoprost taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak area of latanoprost related compound E from the *Sample solution* r_S = peak area of latanoprost related compound E from the *Standard solution* C_S = concentration of USP Latanoprost Related Compound E RS in the *Standard solution* (mg/mL) C_U = concentration of Latanoprost in the *Sample solution* (mg/mL)**Acceptance criteria:** NMT 0.2%**SPECIFIC TESTS****• OPTICAL ROTATION, Specific Rotation <781S>****Sample solution:** 10 mg/mL of Latanoprost in acetonitrile**Acceptance criteria:** +31° to +38°**• WATER DETERMINATION, Method 1c <921>****Sample solution:** 100 mg/mL of Latanoprost in ethyl acetate. [NOTE—Alternatively, *Method 1a* <921> may be used.]**Acceptance criteria:** NMT 2.0%**ADDITIONAL REQUIREMENTS****• PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers, and store in a refrigerator or a freezer.**• USP REFERENCE STANDARDS <11>**

USP Latanoprost RS

USP Latanoprost Related Compound A RS

Isopropyl (E)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate.
C₂₆H₄₀O₅ 432.59

USP Latanoprost Related Compound E RS

(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoic acid.

C₂₃H₃₄O₅ 390.51 ■ 1S (USP36)**Add the following:****• Lopinavir and Ritonavir Tablets****DEFINITION**Lopinavir and Ritonavir Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of lopinavir (C₃₇H₄₈N₄O₅) and ritonavir (C₃₇H₄₈N₆O₅S₂).

IDENTIFICATION

- A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- LOPINAVIR AND RITONAVIR**

Buffer 1: 4.1 g/L of monobasic potassium phosphate in water

Solution A: Acetonitrile and *Buffer 1* (50:50)

Buffer 2: 2.1 g/L of monobasic potassium phosphate in water

Solution B: Acetonitrile and 1-butanol (13:3)

Solution C: Acetonitrile, 1-butanol, *Buffer 1*, and water (65:15:10:10)

Standard solution: 6.25 µg/mL of USP Ritonavir RS and 25 µg/mL of USP Lopinavir RS in *Solution A*

Sample solution: Place a number of Tablets equivalent to 1000 mg of lopinavir and 250 mg of ritonavir in a 250-mL volumetric flask, add 25 mL of *Buffer 2*, and agitate to dissolve the Tablet coating, if necessary. Add 100 mL of *Solution B*, and shake mechanically until the Tablets are dissolved. Dilute with *Solution C* to volume. Centrifuge a portion of this solution, and then further dilute with *Solution A* to a nominal concentration of 6.25 µg/mL of ritonavir and 25 µg/mL of lopinavir.

Mobile phase: Acetonitrile, methanol, tetrahydrofuran, and *Buffer 1* (175:100:100:625)

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

[NOTE—The elution order is ritonavir, then lopinavir.]

Suitability requirements

Capacity factor: 15–24 for the ritonavir peak

Tailing factor: 0.8–1.2 for the ritonavir peak

Theoretical plates: More than 5000 for the ritonavir peak

Relative standard deviation: NMT 2.0% for the ritonavir and lopinavir peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of lopinavir (C₃₇H₄₈N₄O₅) and ritonavir (C₃₇H₄₈N₆O₅S₂) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of lopinavir or ritonavir from the *Sample solution*

r_S = peak response of lopinavir or ritonavir from the *Standard solution*

C_S = concentration of lopinavir or ritonavir in the *Standard solution* (µg/mL)

C_U = nominal concentration of lopinavir or ritonavir in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amounts of lopinavir (C₃₇H₄₈N₄O₅) and ritonavir (C₃₇H₄₈N₆O₅S₂)

PERFORMANCE TESTS

- DISSOLUTION** <711>

Medium: 60 mM polyoxyethylene 10 lauryl ether (37.56 g/L) in water; 900 mL

Apparatus 2: 75 rpm

Time: 90 min

Mobile phase: Acetonitrile and 4.1 g/L potassium phosphate monobasic (55:45). Adjust with phosphoric acid to an apparent pH of 4.0 ± 0.05.

Standard solution: Dissolve USP Lopinavir RS in methanol to obtain a solution containing 2.6 mg/mL. Dissolve USP Ritonavir RS in methanol to obtain a solution containing 1.3 mg/mL. Combine portions of these solutions to make a solution containing approximately 0.104 mg/mL of lopinavir and 0.026 mg/mL of ritonavir in *Medium*.

Sample solutions: Pass a portion of the solution under test through a suitable filter. If necessary, dilute the solution with *Medium* to obtain a final sample solution containing approximately 0.104 mg/mL of lopinavir and 0.026 mg/mL of ritonavir.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between lopinavir and ritonavir

Tailing factor: 0.9–1.5 for the lopinavir and ritonavir peaks

Relative standard deviation: NMT 2.0% for the lopinavir and ritonavir peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of lopinavir (C₃₇H₄₈N₄O₅) and ritonavir (C₃₇H₄₈N₆O₅S₂) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times D \times V \times 100$$

r_U = peak response of lopinavir or ritonavir from the *Sample solution*

r_S = peak response of lopinavir or ritonavir from the *Standard solution*

C_S = concentration of USP Lopinavir RS or USP Ritonavir RS in the *Standard solution* (mg/mL)

L = Tablet label claim for lopinavir or ritonavir (mg)

D = dilution factor of the *Sample solution*

V = volume of *Medium*, 900 mL

Tolerances: NLT 80.0% (Q) of the labeled amounts of lopinavir (C₃₇H₄₈N₄O₅) and ritonavir (C₃₇H₄₈N₆O₅S₂) are dissolved.

- UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

IMPURITIES

- ORGANIC IMPURITIES**

Buffer 1: 4.1 g/L of monobasic potassium phosphate in water

Solution A: *Buffer 1* and acetonitrile (50:50)

Buffer 2: 2.1 g/L of monobasic potassium phosphate in water

Solution B: Acetonitrile, 1-butanol, and *Buffer 1* (15:5:80)

Solution C: Acetonitrile, 1-butanol, *Buffer 1*, and water (65:15:10:10)

Solution D: Acetonitrile and 1-butanol (13:3)

Buffer solution: 3.8 g/L of monobasic potassium phosphate and 0.25 g/L of dibasic potassium phosphate in water

Mobile phase: Acetonitrile, tetrahydrofuran, 1-butanol, and *Buffer solution* (18:8:5:69). Adjust with 1 M phosphoric acid or 1 M potassium hydroxide, if necessary, to a pH of 6.3 ± 0.1.

Standard stock solution: 0.025 mg/mL of USP Ritonavir RS in *Solution A*

Standard solution: 2.5 µg/mL of USP Ritonavir RS in *Solution B* from *Standard stock solution*

Ritonavir degradant identification solution: Transfer two 5.0 mL portions of a 1 mg/mL solution of USP Ritonavir RS in *Solution A* to separate 50-mL volumetric flasks. Add 1 g of citric acid to one flask, and shake until dissolved. Heat both flasks at 80° for approximately 24 h. Cool the flasks, and add 13 mL of 1 N sodium hydroxide to the flask containing the citric acid. Dilute both flasks with *Solution B* to volume. Combine equal volumes of both solutions. This solution contains ritonavir and the ritonavir degradation products (*N*-deacylvaline ritonavir, hydantoin aminoalcohol, *O*-acyl isomer, and oxazolidinone derivative).

Ritonavir related compounds identification solution: 1 mg/mL of USP Ritonavir Related Compounds Mixture RS dissolved in *Solution C* and further diluted with *Solution B* to 0.5 mg/mL.

Sample solution: Place a number of Tablets equivalent to 1000 mg of lopinavir and 250 mg of ritonavir into a 250-mL volumetric flask. Add 25 mL of *Buffer 2*, and agitate to dissolve the Tablet coating, if necessary. Add 100 mL of *Solution D*, and shake mechanically until the Tablets are dissolved. Dilute with *Solution C* to volume. Centrifuge a portion of this solution, and further dilute with *Solution B* to a concentration of 2 mg/mL of lopinavir and 0.5 mg/mL of ritonavir.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Column: 4.6-mm × 15-cm; 3-μm packing L26

Column temperature: 60°

Detector: UV 240 nm

Injection volume: 50 μL

Flow rate: 1.0 mL/min

System suitability

Samples: *Ritonavir degradant identification solution*, *Ritonavir related compounds identification solution*, and *Standard solution*

Suitability requirements

Resolution: NLT 1.0 between the peaks for *O*-acyl isomer and oxazolidinone derivative, *Ritonavir degradant identification solution*. NLT 0.7 between the peaks for hydroxyritonavir and hydantoin aminoalcohol, *Ritonavir related compounds identification solution*

Capacity factor: NLT 10.8, *Standard solution*

Tailing factor: 0.8–1.2, *Standard solution*

Column efficiency: NLT 5000, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each ritonavir degradation product in the *Sample solution*:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

r_u = peak area of individual degradation product from the *Sample solution*

r_s = peak response of ritonavir from the *Standard solution*

C_s = concentration of USP Ritonavir RS in the *Standard solution* (mg/mL)

C_u = nominal concentration of ritonavir in the *Sample solution* (mg/mL)

F = relative response factor

Acceptance criteria: See *Table 1*. [NOTE—Disregard all peaks eluting before the retention time of the *N*-deacylvaline ritonavir peak from the *Ritonavir degradant identification solution*.]

Table 1

Name	Relative Retention	Relative Response Factor	Acceptance Criteria, NMT (%)
<i>N</i> -Deacylvaline ritonavir ^a	0.11	0.81	0.2
Acetamidoalcohol ^b	0.15	—	—*
2,5-Thiazolylmethyl-dicarbamate ^c	0.24	—	—*
Hydroxyritonavir ^d	0.36	0.86	0.3
Hydantoin aminoalcohol ^e	0.39	0.73	2.6
Ritonavir hydroperoxide ^f	0.44	0.88	0.2
Hydantoin-oxazolidinone derivative ^g	0.50	—	—*
Ethyl analog ^h	0.64	—	—*
<i>O</i> -Acyl isomer ⁱ	0.74	1.1	0.2
BOC-aminoalcohol ^j	0.81	—	—*
Isobutoxycarbonyl aminoalcohol ^k	0.81	—	—*
Oxazolidinone derivative ^l	0.87	0.53	0.3

^a Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-[(*S*)-2-amino-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^b Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-acetamido-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^c Bis(thiazol-5-ylmethyl) (2*S*,3*S*,5*S*)-3-hydroxy-1,6-diphenylhexane-2,5-diyl-dicarbamate.

^d Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-3-hydroxy-5-[(*S*)-2-(3-[[2-(2-hydroxypropan-2-yl)thiazol-4-yl]methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^e Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-3-hydroxy-5-[(*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl]-1,6-diphenylhexan-2-ylcarbamate.

^f Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-[(*S*)-2-(3-[[2-(2-hydroperoxypropan-2-yl)thiazol-4-yl]methyl]-3-methylureido)-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^g (4*S*,5*S*)-Thiazol-5-ylmethyl 4-benzyl-5-[(*S*)-2-[(*S*)-4-isopropyl-2,5-dioxoimidazolidin-1-yl]-3-phenylpropyl]-2-oxooxazolidine-3-carboxylate.

^h Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-[(*S*)-2-(3-[[2-ethylthiazol-4-yl]methyl]-3-methylureido)-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

ⁱ (*S*)-[(2*S*,3*S*,5*S*)-5-Amino-1,6-diphenyl-2-[(thiazol-5-ylmethoxy)carbonylamino]hexan-3-yl] 2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanoate.

^j Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-(*t*-butoxycarbonylamino)-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^k Thiazol-5-ylmethyl (2*S*,3*S*,5*S*)-5-(isobutoxycarbonylamino)-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^l (*S*)-*N*-[(*S*)-1-[(4*S*,5*S*)-4-Benzyl-2-oxooxazolidin-5-yl]-3-phenylpropan-2-yl]-2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamide.

^m (*S*)-Isobutyl 2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanoate.

ⁿ Thiazol-5-ylmethyl (2*S*,4*S*,5*S*)-4-hydroxy-5-[(*S*)-2-(3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^o Thiazol-5-ylmethyl (2*S*,3*R*,5*S*)-3-hydroxy-5-[(*S*)-2-(3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^p Bis(thiazol-5-ylmethyl) (2*S*,2'*S*,3*S*,3'*S*,5*S*,5'*S*)-5,5'-carbonylbis(azanediyl)bis(3-hydroxy-1,6-diphenylhexane-5,2-diyl)dicarbamate.

^q Thiazol-5-ylmethyl (2*S*,3*R*,5*R*)-3-hydroxy-5-[(*S*)-2-(3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^r Thiazol-5-ylmethyl (2*S*,3*S*,5*R*)-3-hydroxy-5-[(*S*)-2-(3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^s (3*S*,4*S*,6*S*,10*S*,13*S*,15*S*,16*S*)-Bis(thiazol-5-ylmethyl)-4,15-dihydroxy-10-isopropyl-8,11-dioxo-3,6,13,16-tetrabenzyl-2,7,9,12,17-pentaazaoctadecanedioate.

* Process impurities; for information only.

** Disregard any peak less than 0.05%.

Table 1 (Continued)

Name	Relative Retention	Relative Response Factor	Acceptance Criteria, NMT (%)
Ureidovaline isobutyl ester ^m	0.94	—	—*
Ritonavir	1.0	—	—*
4-Hydroxy isomer ⁿ	1.05	—	—*
3R-Epimer ^o	1.11	—	—*
Aminoalcohol urea derivative ^p	1.14	—	—*
3R,5R-Epimer ^q	1.23	—	—*
5R-Epimer ^r	1.32	—	—*
Diacyl valine urea ^s	1.70	—	—*
Any unspecified impurity	—	1.0	0.2**
Total impurities	—	—	3.5 **

^a Thiazol-5-ylmethyl (2S,3S,5S)-5-[(S)-2-amino-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^b Thiazol-5-ylmethyl (2S,3S,5S)-5-acetamido-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^c Bis(thiazol-5-ylmethyl) (2S,3S,5S)-3-hydroxy-1,6-diphenylhexane-2,5-diylidicarbamate.

^d Thiazol-5-ylmethyl (2S,3S,5S)-3-hydroxy-5-[(S)-2-[(2-hydroxypropan-2-yl)thiazol-4-yl]methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^e Thiazol-5-ylmethyl (2S,3S,5S)-3-hydroxy-5-[(S)-4-isopropyl-2,5-dioximidazolidin-1-yl]-1,6-diphenylhexan-2-ylcarbamate.

^f Thiazol-5-ylmethyl (2S,3S,5S)-5-[(S)-2-[(2-(2-hydroperoxypropan-2-yl)thiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^g (4S,5S)-Thiazol-5-ylmethyl 4-benzyl-5-[(S)-2-[(S)-4-isopropyl-2,5-dioximidazolidin-1-yl]-3-phenylpropyl]-2-oxooxazolidine-3-carboxylate.

^h Thiazol-5-ylmethyl (2S,3S,5S)-5-[(S)-2-[(2-ethylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

ⁱ (S)-[(2S,3S,5S)-5-Amino-1,6-diphenyl-2-[(thiazol-5-ylmethoxy)carbonylamino]hexan-3-yl] 2-[3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanoate.

^j Thiazol-5-ylmethyl (2S,3S,5S)-5-(t-butoxycarbonylamino)-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^k Bis(thiazol-5-ylmethyl) (2S,3S,5S)-5-(isobutoxycarbonylamino)-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^l (S)-N-[(S)-1-[(4S,5S)-4-Benzyl-2-oxooxazolidin-5-yl]-3-phenylpropan-2-yl]-2-[3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamide.

^m (S)-Isobutyl 2-[3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanoate.

ⁿ Thiazol-5-ylmethyl (2S,4S,5S)-4-hydroxy-5-[(S)-2-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^o Thiazol-5-ylmethyl (2S,3R,5S)-3-hydroxy-5-[(S)-2-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^p Bis(thiazol-5-ylmethyl) (2S,2'S,3S,3'S,5S,5'S)-5,5'-carbonylbis(azanediyl)bis(3-hydroxy-1,6-diphenylhexane-5,2-diyl)dicarbamate.

^q Thiazol-5-ylmethyl (2S,3R,5R)-3-hydroxy-5-[(S)-2-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^r Thiazol-5-ylmethyl (2S,3S,5R)-3-hydroxy-5-[(S)-2-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido)-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^s (3S,4S,6S,10S,13S,15S,16S)-Bis(thiazol-5-ylmethyl)-4,15-dihydroxy-10-isopropyl-8,11-dioxo-3,6,13,16-tetrabenzyl-2,7,9,12,17-pentaazaooctadecanedioate.

* Process impurities; for information only.

** Disregard any peak less than 0.05%.

ADDITIONAL REQUIREMENTS

• USP REFERENCE STANDARDS (11)

USP Lopinavir RS

USP Ritonavir RS

USP Ritonavir Related Compounds Mixture RS¹⁵ (USP36)

Lorazepam Oral Concentrate

DEFINITION

Lorazepam Oral Concentrate contains NLT 90.0% and NMT 110.0% of the labeled amount of lorazepam ($C_{15}H_{10}Cl_2N_2O_2$).

IDENTIFICATION

- A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• PROCEDURE

Mobile phase: Acetonitrile, glacial acetic acid, and water (45: 0.2: 55)

Standard solution: 0.05 mg/mL of USP Lorazepam RS in methanol

System suitability solution: 0.1 mg/mL each of USP Lorazepam RS and USP Lorazepam Related Compound E RS in methanol

Sample solution: Nominally 0.05 mg/mL of lorazepam prepared as follows. Transfer a suitable volume of Oral Concentrate to a volumetric flask, and dilute with methanol to volume.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4-mm × 30-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for lorazepam and lorazepam related compound E are 0.6 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between lorazepam and lorazepam related compound E, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of lorazepam ($C_{15}H_{10}Cl_2N_2O_2$) in the portion of Oral Concentrate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Lorazepam RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of lorazepam in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

• ORGANIC IMPURITIES

Mobile phase: Methanol and 0.05 M monobasic ammonium phosphate (64:36)

Diluent: Methanol and 0.05 M monobasic ammonium phosphate (50:50). Adjust with ammonium hydroxide to a pH of 6.5.

Standard stock solution: 1.0 mg/mL USP Lorazepam RS in methanol

Standard solution 1: 0.16 µg/mL of lorazepam from the *Standard stock solution* in *Diluent*

Standard solution 2: 0.16 µg/mL of USP Lorazepam Related Compound B RS, and 3.2 µg/mL each of USP Lorazepam Related Compound C RS and USP Lorazepam Related Compound D RS in *Mobile phase*

System suitability solution: 0.04 mg/mL of USP Lorazepam RS, and 0.032 mg/mL each of USP Lorazepam Related Compound C RS and USP Lorazepam Related Compound D RS in *Diluent*

Sample solution: Nominally 0.16 mg/mL of lorazepam prepared as follows. Transfer a suitable volume of Oral Concentrate to a volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 10- to 15-cm; packing L1

Flow rate: 0.7 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution 1*

Suitability requirements

Resolution: NLT 1.2 between lorazepam related compound D and lorazepam; NLT 1.2 between lorazepam and lorazepam related compound C, *System suitability solution*

Relative standard deviation: NMT 2.0% for lorazepam, *Standard solution 1*

Analysis

Samples: *Standard solution 2* and *Sample solution* [NOTE—Disregard peaks eluting prior to lorazepam related compound D.]

Calculate the percentage of lorazepam related compound B, lorazepam related compound C, and lorazepam related compound D in the portion of Oral Concentrate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of lorazepam related compound B, lorazepam related compound C, or lorazepam related compound D from the *Sample solution*

r_S = peak response of the corresponding related compound from *Standard solution 2*

C_S = concentration of the corresponding related compound in *Standard solution 2* (mg/mL)

C_U = nominal concentration of lorazepam in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Lorazepam related compound D	■0.8■1S (USP36)	4.0 ^a
Lorazepam	1.0	—
Lorazepam related compound C	■2.3■1S (USP36)	4.0 ^a
Lorazepam related compound B	■2.9■1S (USP36)	0.1

^a Includes the sum of lorazepam related compound C and lorazepam related compound D.

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.

• USP REFERENCE STANDARDS <11>

USP Lorazepam RS

USP Lorazepam Related Compound B RS

2-Amino-2',5-dichlorobenzophenone.

C₁₃H₉Cl₂NO 266.13

USP Lorazepam Related Compound C RS

6-Chloro-4-(o-chlorophenyl)-

2-quinazolinecarboxaldehyde.

C₁₅H₈Cl₂N₂O 303.15

USP Lorazepam Related Compound D RS

6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic acid.

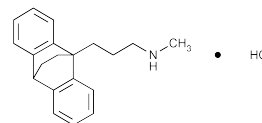
C₁₅H₈Cl₂N₂O₂ 319.15

USP Lorazepam Related Compound E RS

6-Chloro-4-(o-chlorophenyl)-2-quinazoline methanol.

C₁₅H₁₀Cl₂N₂O 305.16

Maprotiline Hydrochloride



C₂₀H₂₃N · HCl 313.86

9,10-Ethanoanthracene-9(10H)-propanamine, N-methyl-, hydrochloride;

N-Methyl-9,10-ethanoanthracene-9(10H)-propylamine hydrochloride [10347-81-6].

DEFINITION

Maprotiline Hydrochloride contains NLT 99.0% and NMT 101.0% of the labeled amount of maprotiline hydrochloride (C₂₀H₂₃N · HCl), calculated on the dried basis.

IDENTIFICATION

- A. INFRARED ABSORPTION** <197K>

- B. ULTRAVIOLET ABSORPTION** <197U>

Sample solution: 100 µg/mL in methanol

Acceptance criteria: Absorptivities at 266 nm and 272 nm, calculated on the dried basis, do not differ by more than 3.0%.

- C. IDENTIFICATION TESTS—GENERAL, Chloride** <191>

Sample solution: 5 mg/mL

Acceptance criteria: Responds to the tests when tested as specified for alkaloidal hydrochloride

ASSAY

- PROCEDURE**

Sample solution: 600 mg of Maprotiline Hydrochloride in 25 mL of mercuric acetate TS

Blank: Mercuric acetate TS

Titrimetric system

(See *Titrimetry* <541>.)

Mode: Potentiometric

Titrat: 0.1 N perchloric acid VS

Analysis: Titrate the *Sample solution* with *Titrat* using a glass electrode and a calomel electrode containing saturated lithium chloride in glacial acetic acid. Perform a blank determination. Each mL of 0.1 N perchloric acid is equivalent to 31.39 mg of maprotiline hydrochloride (C₂₀H₂₃N · HCl).

Acceptance criteria: 99.0%–101.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%
- **HEAVY METALS**, Method II (231): NMT 10 ppm

Change to read:

• ORGANIC IMPURITIES

■ **Mobile phase:** Dissolve 0.6 g of ammonium acetate in 200 mL of water, and add 2 mL of a 70-g/L ammonia solution, 150 mL of 2-propanol, and 650 mL of methanol. The resulting apparent pH value is 8.2–8.4.

■ **Standard solution:** 2 µg/mL of USP Maprotiline Hydrochloride RS in *Mobile phase*

■ **System suitability solution:** 1 mg/mL of USP Maprotiline Hydrochloride RS and 0.1 mg/mL of USP Maprotiline Related Compound D RS in *Mobile phase*

■ **Sample solution:** 1 mg/mL of Maprotiline Hydrochloride in *Mobile phase*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

■ **Mode:** LC

■ **Detector:** UV 272 nm

■ **Column:** 4.6-mm × 25-cm; 5-µm packing L1

■ **Flow rate:** 1 mL/min

■ **Injection volume:** 20 µL

■ **Run time:** 1.5 times the retention time of maprotiline

System suitability

■ **Sample:** *System suitability solution*

Suitability requirements

[NOTE—See *Table 1* for relative retention times.]

■ **Resolution:** 1.8–3.2 between the maprotiline related compound D and maprotiline peaks

[NOTE—If necessary, adjust the pH of the *Mobile phase*, in steps of 0.1 pH unit, by adding a 50% v/v solution of acetic acid if the resolution is less than 1.8, or by adding a 70-g/L solution of ammonia if the resolution is greater than 3.2.]

Analysis

■ **Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Maprotiline Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of any impurity from the *Sample solution*

r_S = peak area of maprotiline from the *Standard solution*

C_S = concentration of USP Maprotiline Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Maprotiline Hydrochloride in the *Sample solution* (mg/mL)

■ **Acceptance criteria:** See *Table 1*. Disregard any peak representing less than 0.05% of the area of the main peak.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Maprotiline acrylaldehyde analog ¹	0.3	0.2
Maprotiline dimer ²	0.5	0.2
Desmethylmaprotiline ³	0.7	0.2
Maprotiline related compound D ⁴	0.8	0.2
Maprotiline	1.0	—
N-Methylmaprotiline ⁵	1.3	0.2
Any individual unknown impurity	—	0.10
Total impurities	—	1.0

¹ 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)acrylaldehyde (EP Impurity A).

² N-Methyl-N,N-bis[3-(9,10-dihydro-9,10-ethanoanthracen-9-yl)propyl]amine (EP Impurity B).

³ 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)propan-1-amine (EP Impurity C).

⁴ 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)-N-methylprop-2-en-1-amine (EP Impurity D).

⁵ 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)-N,N-dimethylpropan-1-amine (EP Impurity E).

■ **IS (USP36)**

SPECIFIC TESTS

• LOSS ON DRYING (731)

■ **Sample:** Dry a sample under vacuum at 80° to constant weight.

■ **Acceptance criteria:** NMT 1.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

• USP REFERENCE STANDARDS (11)

■ USP Maprotiline Hydrochloride RS

■ USP Maprotiline Related Compound D RS

3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)-N-methylprop-2-en-1-amine.

C₂₀H₂₂N 276.4 ■ **IS (USP36)**

Delete the following:

Menotropins

DEFINITION

Menotropins is an extract of human post-menopausal urine containing both follicle-stimulating hormone and luteinizing hormone, having the property in females of stimulating growth and maturation of ovarian follicles and the properties in males of maintaining and stimulating testicular interstitial cells (Leydig tissue) related to testosterone production and of being responsible for the full development and maturation of spermatozoa in the seminiferous tubules. It has a potency of NLT 40 USP Follicle-Stimulating Hormone Units and NLT 40 USP Luteinizing Hormone Units per mg, and it contains NLT 80% and NMT 125% of each of the hormone potencies stated on the label. The ratio of Units of Follicle-Stimulating Hormone to Units of Luteinizing Hormone is approximately 1. When necessary, Chorionic Gonadotropin obtained from the urine of pregnant women may be added to achieve this ratio. NMT

30% of the luteinizing hormone activity is contributed by Chorionic Gonadotropin, as determined by a validated method.

ASSAY

• LUTEINIZING HORMONE

Diluent: 10.75 mg/mL of dibasic sodium phosphate, 7.6 mg/mL of sodium chloride, and 1.0 mg/mL of bovine serum albumin in freshly distilled water. Adjust the pH to 7.2 ± 0.2 with 1 N sodium hydroxide, or dilute with 20% phosphoric acid.

Standard solutions: Dissolve USP Menotropins RS in the *Diluent* to obtain solutions having known concentrations of 8.75, 17.5, and 35.0 USP Luteinizing Hormone Units/mL.

Sample solutions: Dissolve Menotropins in the *Diluent* to obtain solutions having concentrations of 8.75, 17.5, and 35.0 USP Luteinizing Hormone Units/mL.

Control solution: *Diluent*

[NOTE—Store all solutions at $5 \pm 3^\circ$ for the duration of the assay, and properly dispose of any unused portions.]

Test animals: Select 20- to 21-day-old male rats with weights within a 10-g range of each other. House the animals under uniform conditions of temperature, light, food, and water. Mark the animals for identification, and divide them at random into 7 groups of the same number, having NLT 6 animals/group. Assign one group to each *Standard solution*, one group to each *Sample solution*, and one group to the *Control solution*.

Dose determination trial: Use the method described for *Procedure* to determine a 3-dose range in which the lowest dose produces a definite response in some of the rats in the low-dose group (as compared with the control group) and the highest dose produces a submaximal to maximal response in the high-dose group. Doses must be established in a geometric progression. The normal dose response range will occur between 3.5 and 28 USP Luteinizing Hormone Units total dose/rat. Useful dose ranges will vary with the sensitivity of the rat strain selected.

Procedure: Inject each rat of each group subcutaneously in the dorsal area with 0.2 mL of the solution to which it was assigned. For the *Dose determination trial* only, similarly inject each rat in the control group with 0.2 mL of the *Control solution*. Repeat these injections at approximately the same time of day after 24, 48, and 72 h. Twenty-four h after the last injection, weigh each rat, sacrifice the animals, and carefully dissect out the seminal vesicle of each rat, removing any fat and fibrous tissue. Thoroughly dry the vesicles by pressing against absorbent paper, avoiding damage to the vesicles, and immediately weigh them to the nearest 0.2 mg, using a suitable balance.

Calculation: Tabulate the observed seminal vesicle weights (y) for each dosage group of f rats. For apparently outlying seminal vesicle weights, an attempt may be made to correct the organ mass relative to the mass of the rat from which it was taken. For the y -value in question, calculate for each of the f rats in the appropriate group the ratio of seminal vesicle weight to total body weight. Reject the y -value if its corresponding ratio differs from the rest of the group by more than 1.5 standard deviations.

If the data from one or more rats are missing, adjust to groups of equal size by suitable means (see *Design and Analysis of Biological Assays* (111), *Replacement of Missing Values*). Total the values of y in each group, and designate each total as T , using subscripts 1 to 3 for the three successive dosage levels and subscripts S and U for the Standard and the material under test, respectively. Test both the agreement in slope of the dosage-response lines for the Standard and for the material under test, and the lack of curvature as directed for a 3-dose balanced assay (see *Design and*

Analysis of Biological Assays (111), *Tests of Assay Validity*). If the combined discrepancy as measured by F_3 exceeds its tabular value in Table 9, repeat the assay. Determine the logarithm of luteinizing hormone potency of the Menotropins taken:

$$M = (4iT_A/3T_B) + \log R$$

$$T_A = \sum(T_U - T_S)$$

$$T_B = \sum(T_3 - T_1)$$

i = interval between successive log doses of both the *Standard solution* and the *Sample solution*

R = v_S/v_U , the ratio of the high dose of the Standard in USP Luteinizing Hormone Units (v_S) to the high dose of the Menotropins (v_U), in mg

Compute the log confidence interval (see *Design and Analysis of Biological Assays* (111)).

Replication: Repeat the entire determination at least once. Test the agreement among the two or more independent determinations, and compute the weight for each (see *Combination of Independent Assays* (111)). Calculate the weighted mean log-potency M and its confidence interval, L_c (see *Confidence Intervals for Individual Assays* (111)). The potency, P^* , is satisfactory if $P^* = \text{antilog } M$ is NLT 80% and NMT 125% of the labeled potency and if the confidence interval does not exceed 0.18.

• FOLLICLE-STIMULATING HORMONE

Diluting solution: Using the *Diluent* in the *Assay for Luteinizing Hormone*, dissolve USP Human Chorionic Gonadotropin RS in *Diluent* to obtain a solution having a concentration of 70 USP Chorionic Gonadotropin Units/mL, readjusting the pH, if necessary, to 7.2 ± 0.2 .

Standard solutions: Dissolve USP Menotropins RS in the *Diluting solution* to obtain solutions having known concentrations of 2.5, 5.0, and 10.0 USP Follicle-Stimulating Hormone Units/mL.

Sample solutions: Dissolve Menotropins in the *Diluting solution* to obtain solutions having concentrations of 2.5, 5.0, and 10.0 USP Follicle-Stimulating Hormone Units/mL.

Control solution: *Diluting solution*

[NOTE—Store all solutions at $5 \pm 3^\circ$ for the duration of the assay, and properly dispose of any unused portions.]

Test animals: Select 20- to 21-day-old female rats with weights within a 10-g range of each other. Proceed as directed under *Test animals* in the *Assay for Luteinizing Hormone* beginning with "House the animals".

Dose determination trial: Use the method described for *Procedure* to determine a 3-dose range in which the lowest dose produces a definite response in some of the rats in the low-dose group (as compared with the control group) and the highest dose produces a submaximal to maximal response in the high-dose group. Doses must be established in a geometric progression. The normal dose response range will occur between 0.5 and 6.0 USP Follicle-Stimulating Hormone Units total dose/rat. Useful dose ranges will vary with the sensitivity of the rat strain selected.

Procedure: Inject each rat of each group subcutaneously in the dorsal area with 0.2 mL of the solution to which it was assigned. For *Dose determination trial* only, similarly inject each rat in the control group with 0.2 mL of the *Control solution*. Repeat these injections at approximately the same time of day after 24 and 48 h. Twenty-four h after the last injection, weigh each rat, sacrifice the animals, and carefully dissect out the ovaries of each rat, removing any fat and fibrous tissue. Thoroughly dry the ovaries by pressing against absorbent paper, avoiding damage to follicles on the ovary surface, and immediately weigh them to the nearest 0.2 mg, using a suitable balance.

Calculation: Tabulate the observed ovarian pair weight for each rat designated by the symbol y , for each dosage group of f rats. For apparently outlying ovarian weight gain, an attempt may be made to correct the organ mass relative to the mass of the rat from which it was taken. For the y -value in question, calculate for each of the f rats in the appropriate group the ratio of ovarian weight to the total body weight. Reject the y -value if its corresponding ratio differs from the rest of the group by more than 1.5 standard deviations.

If the data from one or more rats are missing, adjust to groups of equal size by suitable means (see *Design and Analysis of Biological Assays* (111), *Replacement of Missing Values*). Total the values of y in each group, and designate each total as T , using subscripts 1 to 3 for the three successive dosage levels and subscripts S and U for the Standard and the material under test, respectively. Test both the agreement in slope of the dosage–response lines for the Standard and for the material under test, and the lack of curvature as directed for a 3-dose balanced assay (see *Design and Analysis of Biological Assays* (111), *Tests of Assay Validity*). If the combined discrepancy as measured by F_3 exceeds its tabular value in Table 9 (see *Design and Analysis of Biological Assays* (111), *Combination of Independent Assays*), regard these data as preliminary, and repeat the assay.

Determine the logarithm of follicle-stimulating hormone potency of the Menotropins taken:

$$M = (4iT_A/3T_B) + \log R$$

$$\begin{aligned} T_A &= \Sigma(T_U - T_S) \\ T_B &= \Sigma(T_3 - T_1) \end{aligned}$$

i = interval between successive log doses of both the *Standard solution* and *Sample solution*

R = v_S/v_U , the ratio of the high dose of the Standard in USP Units (v_S) to the high dose of the Menotropins (v_U), in mg

Compute the log confidence interval (see *Design and Analysis of Biological Assays* (111)).

Replication: Repeat the entire determination at least once. Test the agreement among the two or more independent determinations, and compute the weights/mean log-potency M and its confidence interval, L_c (see *Design and Analysis of Biological Assays* (111), *Confidence Intervals for Individual Assays*). If this exceeds 0.18, repeat the assay until the confidence interval of the combined results is 0.18 or less. The potency P^* is satisfactory if $P^* = \text{antilog } M$ is NLT 80% and NMT 125% of the labeled potency and if the log confidence interval does not exceed 0.18.

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST (85):** It contains NMT 2.5 Endotoxin Units/USP Follicle-Stimulating Hormone Unit.

SAFETY

Sample solution: Prepare a Menotropin solution with *Sodium Chloride Injection* containing 75 USP Follicle-Stimulating Hormone Units/mL.

Procedure: Select 5 healthy mice, each weighing between 18 and 22 g. Inject intravenously one dose of 1.0 mL of the *Sample solution* into each of the mice. Observe the animals over the 48 h following the injection. If, at the end of 48 h, NMT 1 of the animals shows outward symptoms of a toxic reaction, the requirements of the test are met. If 1 or 2 of the animals die, repeat the test on 10 additional, similar animals.

Acceptance criteria: If all of the animals survive for 48 h and show no symptoms of a toxic reaction, the requirements of the test are met.

- **WATER DETERMINATION, Method I (921):** NMT 5.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, preferably of Type I glass, and store in a refrigerator.
- **USP REFERENCE STANDARDS (11)**
 - USP Endotoxin RS
 - USP Human Chorionic Gonadotropin RS
 - USP Menotropins RS¹⁵ (USP36)

Delete the following:

Menotropins for Injection

DEFINITION

Menotropins for Injection is a sterile, freeze-dried mixture of menotropins and suitable excipients. Its potency is NLT 80% and NMT 125% of each of the Follicle-Stimulating Hormone and Luteinizing Hormone potencies stated on the label. It may contain an antimicrobial agent.

ASSAY

LUTEINIZING HORMONE

Diluent: 10.75 mg/mL of dibasic sodium phosphate, 7.6 mg/mL of sodium chloride, and 1.0 mg/mL of bovine serum albumin in freshly distilled water. Adjust the pH to 7.2 ± 0.2 with 1 N sodium hydroxide or dilute with 20% phosphoric acid.

Standard solutions: Dissolve USP Menotropins RS in the *Diluent* to obtain solutions having known concentrations of 8.75, 17.5, and 35.0 USP Luteinizing Hormone Units/mL.

Sample solutions: Dissolve Menotropins for Injection in the *Diluent* to obtain solutions having concentrations of 8.75, 17.5, and 35.0 USP Luteinizing Hormone Units/mL.

Control solution: *Diluent*

[NOTE—Store all solutions at $5 \pm 3^\circ$ for the duration of the assay and properly dispose of any unused portions.]

Test animals: Select 20- to 21-day-old male rats with weights within a 10-g range of each other. House the animals under uniform conditions of temperature, light, food, and water. Mark the animals for identification, and divide them at random into 7 groups of the same number, having NLT 6 animals/group. Assign one group to each *Standard solution*, one group to each *Sample solution*, and one group to the *Control solution*.

Dose determination trial: Use the method described for *Procedure* to determine a 3-dose range in which the lowest dose produces a definite response in some of the rats in the low-dose group (as compared with the control group) and the highest dose produces a submaximal to maximal response in the high-dose group. Doses must be established in a geometric progression. The normal dose response range will occur between 3.5 and 28 USP Luteinizing Hormone Units total dose/rat. Useful dose ranges will vary with the sensitivity of the rat strain selected.

Procedure: Inject each rat of each group subcutaneously in the dorsal area with 0.2 mL of the solution to which it was assigned. For the *Dose determination trial* only, similarly inject each rat in the control group with 0.2 mL of the *Control solution*. Repeat these injections at approximately the same time of day after 24, 48, and 72 h. Twenty-four h after the last injection, weigh each rat, sacrifice the animals, and carefully dissect out the seminal vesicle of each rat, removing any fat and fibrous tissue. Thoroughly dry the vesicles by pressing against absorbent paper, avoiding damage to the vesi-

cles, and immediately weigh them to the nearest 0.2 mg, using a suitable balance.

Calculation: Tabulate the observed seminal vesicle weights (y) for each dosage group of f rats. For apparently outlying seminal vesicle weights, an attempt may be made to correct the organ mass relative to the mass of the rat from which it was taken. For the y -value in question, calculate for each of the f rats in the appropriate group the ratio of seminal vesicle weight to total body weight. Reject the y -value if its corresponding ratio differs from the rest of the group by more than 1.5 standard deviations.

If the data from one or more rats are missing, adjust to groups of equal size by suitable means (see *Design and Analysis of Biological Assays* (111), *Replacement of Missing Values*). Total the values of y in each group, and designate each total as T , using subscripts 1 to 3 for the three successive dosage levels and subscripts S and U for the Standard and the material under test, respectively. Test both the agreement in slope of the dosage–response lines for the Standard and for the material under test, and the lack of curvature as directed for a 3-dose balanced assay (see *Design and Analysis of Biological Assays* (111), *Tests of Assay Validity*). If the combined discrepancy as measured by F_3 exceeds its tabular value in Table 9, repeat the assay. Determine the logarithm of luteinizing hormone potency of the Menotropins taken:

$$M = (4iT_A/3T_B) + \log R$$

$$\frac{T_A}{T_B} = \frac{\Sigma(T_U - T_S)}{\Sigma(T_3 - T_1)}$$

i = interval between successive log doses of both the Standard solution and the Sample solution

R = v_S/v_U , the ratio of the high dose of the Standard in USP Luteinizing Hormone Units (v_S) to the high dose of the Menotropins (v_U), in mg

Compute the log confidence interval (see *Design and Analysis of Biological Assays* (111)).

Replication: Repeat the entire determination at least once. Test the agreement among the two or more independent determinations, and compute the weight for each (see *Combination of Independent Assays* (111)). Calculate the weighted mean log-potency M and its confidence interval, L_c (see *Confidence Intervals for Individual Assays* (111)). The potency, P^* , is satisfactory if $P^* = \text{antilog } M$ is NLT 80% and NMT 125% of the labeled potency and if the confidence interval does not exceed 0.18.

• FOLLICLE-STIMULATING HORMONE

Diluting solution: Using the *Diluent* under Assay for Luteinizing Hormone, dissolve USP Human Chorionic Gonadotropin RS in *Diluent* to obtain a solution having a concentration of 70 USP Chorionic Gonadotropin Units/mL, readjusting the pH, if necessary, to 7.2 ± 0.2 .

Standard solutions: Dissolve USP Menotropins RS in the *Diluting solution* to obtain solutions having concentrations of 2.5, 5.0, and 10.0 USP Follicle-Stimulating Hormone Units/mL.

Sample solutions: Dissolve Menotropins for Injection in the *Diluting solution* to obtain solutions having concentrations of 2.5, 5.0, and 10.0 USP Follicle-Stimulating Hormone Units/mL.

Control solution: *Diluting solution*

[NOTE—Store all solutions at $5 \pm 3^\circ$ for the duration of the assay, and properly dispose of any unused portions.]

Test animals: Select 20- to 21-day-old female rats with weights within a 10-g range of each other. Proceed as directed under *Test animals* in the Assay for Luteinizing Hormone beginning with “House the animals”.

Dose determination trial: Use the method described for *Procedure* to determine a 3-dose range in which the

lowest dose produces a definite response in some of the rats in the low-dose group (as compared with the control group) and the highest dose produces a submaximal to maximal response in the high-dose group.

Doses must be established in a geometric progression. The normal dose response range will occur between 0.5 and 6.0 USP Follicle-Stimulating Hormone Units total dose/rat. Useful dose ranges will vary with the sensitivity of the rat strain selected.

Procedure: Inject each rat of each group subcutaneously in the dorsal area with 0.2 mL of the solution to which it was assigned. For *Dose determination trial* only, similarly inject each rat in the control group with 0.2 mL of the *Control solution*. Repeat these injections at approximately the same time of day after 24 and 48 h. Twenty-four h after the last injection, weigh each rat, sacrifice the animals, and carefully dissect out the ovaries of each rat, removing any fat and fibrous tissue. Thoroughly dry the ovaries by pressing against absorbent paper, avoiding damage to follicles on the ovary surface, and immediately weigh them to the nearest 0.2 mg, using a suitable balance.

Calculation: Tabulate the observed ovarian pair weight for each rat designated by the symbol y , for each dosage group of f rats. For apparently outlying ovarian weight gain, an attempt may be made to correct the organ mass relative to the mass of the rat from which it was taken. For the y -value in question, calculate for each of the f rats in the appropriate group the ratio of ovarian weight to the total body weight. Reject the y -value if its corresponding ratio differs from the rest of the group by more than 1.5 standard deviations. If the data from one or more rats are missing, adjust to groups of equal size by suitable means (see *Design and Analysis of Biological Assays* (111), *Replacement of Missing Values*). Total the values of y in each group, and designate each total as T , using subscripts 1 to 3 for the three successive dosage levels and subscripts S and U for the Standard and the material under test, respectively. Test both the agreement in slope of the dosage–response lines for the Standard and for the material under test, and the lack of curvature as directed for a 3-dose balanced assay (see *Design and Analysis of Biological Assays* (111), *Tests of Assay Validity*). If the combined discrepancy as measured by F_3 exceeds its tabular value in Table 9 (see *Design and Analysis of Biological Assays* (111), *Combination of Independent Assays*), regard these data as preliminary, and repeat the assay. Determine the logarithm of follicle-stimulating hormone potency of the Menotropins taken:

$$M = (4iT_A/3T_B) + \log R$$

$$\frac{T_A}{T_B} = \frac{\Sigma(T_U - T_S)}{\Sigma(T_3 - T_1)}$$

i = interval between successive log doses of both the Standard solution and Sample solution

R = v_S/v_U , the ratio of the high dose of the Standard in USP Units (v_S) to the high dose of the Menotropins (v_U), in mg

Compute the log confidence interval (see *Design and Analysis of Biological Assays* (111)).

Replication: Repeat the entire determination at least once. Test the agreement among the two or more independent determinations, and compute the weights/mean log-potency M and its confidence interval, L_c (see *Design and Analysis of Biological Assays* (111), *Confidence Intervals for Individual Assays*). If this exceeds 0.18, repeat the assay until the confidence interval of the combined results is 0.18 or less. The potency P^* is satisfactory if $P^* = \text{antilog } M$ is NLT 80% and NMT 125% of the labeled potency and if the log confidence interval does not exceed 0.18.

PERFORMANCE TESTS

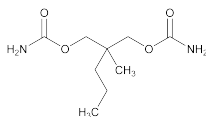
- **UNIFORMITY OF DOSAGE UNITS (905):** Open 10 containers and weigh each individual container and its contents, taking care to preserve the identity of each container. Remove the contents of each container by rinsing thoroughly with water, dry at 105° to constant weight, and reweigh. Calculate for each container the net weight of its contents by subtracting the weight of the dry, empty container from its initial gross weight. Determine the average weight of the contents and the relative standard deviation (see *Calculation of the Relative Standard Deviation*). The requirements are met if the weight of the contents of each container does not deviate from the average weight by more than 5.0% and the relative standard deviation of the 10 containers is NMT 3.0%. If the requirements of the test are not met, test 20 additional containers. The requirements are met if the net weight of NMT 1 container of the 30 deviates by more than 7.5% from the average weight of the contents of the 30 containers and the relative standard deviation of the 30 containers is NMT 3.3%.

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST (85):** It contains NMT 2.5 USP Endotoxin Units/USP Follicle-stimulating Hormone Unit.
- **CONSTITUTED SOLUTION:** At the time of use, it meets the requirements for *Injections* (1), *Constituted Solutions*.
- **PH (791):** 6.0–7.0, in the solution constituted as directed in the labeling
- **STERILITY TESTS (71):** Meets the requirements
- **OTHER REQUIREMENTS:** It meets the requirements under *Injections* (1), *Labeling*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve as described under *Injections* (1), *Containers for Sterile Solids*.
- **USP REFERENCE STANDARDS (11)**
USP Endotoxin RS
USP Human Chorionic Gonadotropin RS
USP Menotropins RS[■]_{1S} (USP36)

Meprobamate

C₉H₁₈N₂O₄ 218.25
1,3-Propanediol, 2-methyl-2-propyl-, dicarbamate;
2-Methyl-2-propyl-1,3-propanediol dicarbamate [57-53-4].

DEFINITION

Meprobamate contains NLT 97.0% and NMT 101.0% of meprobamate (C₉H₁₈N₂O₄), calculated on the dried basis.

IDENTIFICATION**Change to read:**

- **A. ■INFRARED ABSORPTION (197K)**[■]_{1S} (USP36)
Sample: 1 mg in 200 mg
Acceptance criteria: The IR absorption spectrum of a potassium bromide dispersion of the *Sample*, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Meprobamate RS. If

a difference appears, dissolve portions of both the *Sample* and the Reference Standard in acetone at a concentration of 8 mg/mL. Dilute 0.1-mL portions of the acetone solutions with 1 mL of *n*-heptane, and remove the solvents by evaporation under nitrogen at a temperature of 30°. Dry the residues under vacuum at room temperature for 30 min, and repeat the test on the residues.

Change to read:

- **B. ■**The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.[■]_{1S} (USP36)

ASSAY**Change to read:****PROCEDURE**

■**Mobile phase:** Acetonitrile and water (30:70)

■**Standard solution:** 5 mg/mL of USP Meprobamate RS prepared as follows. Dissolve the Standard first in acetonitrile using 30% of final volume. Sonicate if necessary to dissolve, and cool to room temperature. Dilute with water to volume.

■**Sample solution:** 5 mg/mL of Meprobamate prepared as follows. Dissolve the sample first in acetonitrile using 30% of final volume. Sonicate if necessary to dissolve, and cool to room temperature. Dilute with water to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

■**Mode:** LC

■**Detector:** UV 200 nm

■**Column:** 4.6-mm × 25-cm; 4-μm packing L1

■**Flow rate:** 1 mL/min

■**Injection volume:** 20 μL

■**Run time:** 2 times the retention time of meprobamate

System suitability

■**Sample:** *Standard solution*

Suitability requirements

■**Tailing factor:** NMT 2.0

■**Relative standard deviation:** NMT 2.0%

Analysis

■**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of meprobamate (C₉H₁₈N₂O₄) in the portion of Meprobamate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

■ r_U = peak response from the *Sample solution*

■ r_S = peak response from the *Standard solution*

■ C_S = concentration of USP Meprobamate RS in the *Standard solution* (mg/mL)

■ C_U = concentration of Meprobamate in the *Sample solution* (mg/mL)[■]_{1S} (USP36)

■**Acceptance criteria:** 97.0%–101.0% on the dried basis

IMPURITIES**Change to read:****ORGANIC IMPURITIES: PROCEDURE 1**

■**Standard solutions:** Dissolve USP Meprobamate RS in alcohol, and mix to obtain *Standard solution A* with a known concentration of 1.0 mg/mL. Dilute quantitatively with alcohol to obtain the *Standard solutions* with the compositions given in *Table 1*.

Table 1

Standard Solution	Dilution	Concentration (mg RS/mL)	Percentage (% for Comparison with Sample)
A	(Undiluted)	1.0	1.0
B	(4 in 5)	0.8	0.8
C	(3 in 5)	0.6	0.6
D	(2 in 5)	0.4	0.4
E	(1 in 5)	0.2	0.2

Sample solution: 100 mg/mL of Meprobamate in alcohol

■^{1S} (USP36)

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: Thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel

Application volume: 2 µL

Developing solvent system: Hexane, acetone, and pyridine (70:30:10)

Spray reagent: 5 mg/mL of vanillin in a cooled mixture of sulfuric acid and alcohol (80:20)

Analysis

Samples: *Standard solutions* and *Sample solution*

■^{1S} (USP36)

Position the plate in a chromatographic chamber, and develop the chromatograms in the *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and air-dry the plate for 15 min. Heat the plate at 100° for 15 min, cool, and spray with *Spray reagent*. Heat the plate at 110° for 15–20 min, cool, and allow the plate to develop blue-purple spots at room temperature. [NOTE—Color development requires about 30–60 min.] Examine the plate, and compare the intensities of any secondary spots of the *Sample solution* with those of the principal spots of the *Standard solutions*.

Acceptance criteria: No secondary spot of the *Sample solution* is larger or more intense than the principal spot of *Standard solution A* (1.0%), and the sum of the intensities of all secondary spots of the *Sample solution* corresponds to NMT 2.0%.

• ORGANIC IMPURITIES, PROCEDURE 2: LIMIT OF METHYL CARBAMATE

Standard solution: 1.0 mg/mL of methyl carbamate

Sample solution: Transfer 1.0 g of finely powdered Meprobamate to a beaker, add 5.0 mL of water, and stir to wet the powder completely. Filter the slurry through a small plug of glass wool in the stem of a glass funnel. Use the clear filtrate.

Mobile phase: Water

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 200 nm

Column: 3.9–4.6-mm × 25–30-cm; packing L1

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Acceptance criteria: The peak response of the *Sample solution* is not greater than that of the *Standard solution*, corresponding to NMT 0.5% of methyl carbamate.

SPECIFIC TESTS

• LOSS ON DRYING <731>

Analysis: Dry a sample under vacuum at 60° for 3 h.

Acceptance criteria: NMT 0.5%

• MELTING RANGE OR TEMPERATURE <741>

103°–107°, but the range between the beginning and end of melting is NMT 2°.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

• **USP REFERENCE STANDARDS <11>**

USP Meprobamate RS

Meprobamate Tablets

DEFINITION

Meprobamate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of meprobamate (C₉H₁₈N₂O₄).

IDENTIFICATION

Change to read:

• A. ■ INFRARED ABSORPTION <197K> ■^{1S} (USP36)

■**Sample:** A portion of finely powdered Tablets, equivalent to 800 mg of meprobamate

Analysis: To the *Sample* add 5 mL of dehydrated alcohol, and heat to just below boiling for about 5 min, with occasional swirling. Cool, and filter into 15 mL of solvent hexane. With the aid of suction, filter the crystals that form, and dry at 60°.

Acceptance criteria: The IR absorption spectrum of a potassium bromide dispersion (about 1 mg in 200 mg) from a portion of crystals obtained from the *Sample* exhibits maxima only at the same wavelengths as that of a similar preparation of USP Meprobamate RS. If a difference appears, dissolve portions of both the *Sample* and the Reference Standard in acetone at a concentration of 8 mg/mL. Dilute 0.1-mL portions of the acetone solutions with 1 mL of *n*-heptane, and remove the solvents by evaporation under nitrogen at a temperature of about 30°. Dry the residues under vacuum at room temperature for 30 min, and repeat the test on the residues. ■^{1S} (USP36)

Change to read:

• **B.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■^{1S} (USP36)

ASSAY

Change to read:

• PROCEDURE

Mobile phase: Acetonitrile and water (30:70)

Phenacetin stock solution: 125 µg/mL of phenacetin in acetonitrile

Phenacetin solution: 25 µg/mL of phenacetin prepared as follows from the *Phenacetin stock solution*. Pipet a suitable volume of *Phenacetin stock solution* into a volumetric flask. Add acetonitrile to fill 30% of the final flask volume, and dilute with water to volume.

Standard solution: 5 mg/mL of USP Meprobamate RS prepared as follows. ■ Transfer a suitable amount of the Reference Standard to a suitable volumetric flask.

■^{1S} (USP36) Dissolve in ■30% ■^{1S} (USP36) of the final flask volume, and dilute with water to volume.

System suitability solution: 5 mg/mL of USP Meprobamate RS and 5 µg/mL of phenacetin prepared as follows. Dissolve a weighed amount of USP Meprobamate RS, first in acetonitrile, using 20% final volume. Shake to dissolve. Add a suitable volume of *Phenacetin solution*, and dilute with water to volume.

Sample solution: Nominally equivalent to 5 mg/mL of meprobamate prepared as follows. Transfer an amount of meprobamate from a portion of finely powdered Tablets (NLT 20) to a suitable volumetric flask. Add acetonitrile to fill 30% of final volume, and shake to dissolve. Dilute with water to volume, and filter, discarding the first 10 mL of the filtrate.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 200 nm

Column: 3.9–4.6-mm × 25–30-cm; 5-µm_{1S} (USP36) packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for meprobamate and phenacetin are about 0.7 and 1.0, respectively.]

Suitability requirements

■_{1S} (USP36)

Resolution: NLT 2.0 between the meprobamate and the phenacetin peaks, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of meprobamate (C₉H₁₈N₂O₄) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of meprobamate from the *Sample solution*

r_S = peak response of meprobamate from the *Standard solution*

C_S = concentration of USP Meprobamate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of meprobamate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION <711>

Procedure for a pooled sample

Medium: Deaerated water; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Standard solution, System suitability solution, Chromatographic system, and System suitability: Proceed as directed in the *Assay*.

Analysis

■ Calculate the percentage of the labeled amount of meprobamate (C₉H₁₈N₂O₄) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Meprobamate RS in the *Standard solution* (mg/mL)

V = volume of the *Medium*, 900 mL

L = label claim (mg/Tablet) ■_{1S} (USP36)

Acceptance criteria: NLT 75% (Q) of the labeled amount of meprobamate (C₉H₁₈N₂O₄) is dissolved.

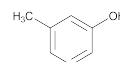
- **UNIFORMITY OF DOSAGE UNITS <905>:** Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.

- **USP REFERENCE STANDARDS <11>**
USP Meprobamate RS

Metacresol



C₇H₈O

3-Methylphenol;

3-Hydroxytoluene [108-39-4].

108.14

DEFINITION

Change to read:

Metacresol contains ■NLT 98.0% and NMT 102.0% ■_{1S} (USP36) of metacresol (C₇H₈O).

IDENTIFICATION

Delete the following:

■ A.

Sample: 10 mL

Analysis: Shake the *Sample* with 30 mL of water in a separator, and allow to separate. The lower layer is clear; the upper layer clears slowly.

Acceptance criteria: To 5 mL of the upper layer add a drop of ferric chloride TS; a bluish color is produced. To a separate 5-mL portion of the upper layer add bromine TS dropwise; a white precipitate is obtained. ■_{1S} (USP36)

Add the following:

■ A. INFRARED ABSORPTION <197F> ■_{1S} (USP36)

Add the following:

- B. The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■_{1S} (USP36)

ASSAY

Change to read:

• PROCEDURE

■ **Internal standard solution:** 1 mg/mL of USP Phenol RS in methanol

System suitability solution: 5 mg/mL each of metacresol, orthocresol, and paracresol in methanol

Standard solution: 1 mg/mL of USP Metacresol RS in the *Internal standard solution*

Sample solution: 1 mg/mL of Metacresol in the *Internal standard solution*

Chromatographic system(See *Chromatography* <621>, *System Suitability*.)**Mode:** GC**Detector:** Flame-ionization**Column:** 0.25-mm × 30-m; 0.25-μm coating of G7**Temperatures****Injection port:** 200°**Detector:** 200°**Column:** See *Table 1*.**Table 1**

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
90	0	90	10
90	2	120	0
120	10	150	3

Carrier gas: Helium**Flow rate:** 1.8 mL/min**Injection type:** Split ratio of 1:40**Injection volume:** 1 μL**System suitability****Samples:** *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for phenol, orthocresol, paracresol, and metacresol are about 0.77, 0.85, 0.99, and 1.00, respectively.]

Suitability requirements**Resolution:** NLT 1.4 between the paracresol and metacresol peaks, *System suitability solution***Relative standard deviation:** NMT 1.0% for the peak ratio of metacresol to phenol, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of metacresol (C₇H₈O) in the portion of Metacresol taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

 R_U = ratio of the metacresol peak response to the phenol peak response from the *Sample solution* R_S = ratio of the metacresol peak response to the phenol peak response from the *Standard solution* C_S = concentration of USP Metacresol RS in the *Standard solution* (mg/mL) C_U = concentration of Metacresol in the *Sample solution* (mg/mL)**Acceptance criteria:** 98.0%–102.0%^{■1S} (USP36)**IMPURITIES****Change to read:****• ORGANIC IMPURITIES****System suitability solution:** 5 mg/mL each of metacresol, orthocresol, and paracresol in methanol**Sensitivity solution:** 5 μg/mL of [■]USP Metacresol RS^{■1S} (USP36) in methanol**Sample solution:** 10 mg/mL of Metacresol in methanol**Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** GC**Detector:** Flame-ionization**Column:** 0.25-mm × 30-m; 0.25-μm coating of G7**Temperatures****Injection port:** 200°**Detector:** 200°**Column:** See *Table 2*.^{■1S} (USP36)**Table 2**^{■1S} (USP36)

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
90	0	90	10
90	2	150	15

Carrier gas: Helium**Flow rate:** 1.8 mL/min**Injection type:** Split ratio of 1:40**Injection volume:** 1 μL**System suitability****Samples:** *System suitability solution* and *Sensitivity solution***Suitability requirements****Resolution:** NLT 1.4 between the paracresol and metacresol peaks, *System suitability solution***Signal-to-noise ratio:** NLT 10, *Sensitivity solution***Analysis****Sample:** *Sample solution*

Calculate the percentage of each individual impurity in the portion of Metacresol taken:

$$\text{Result} = (r_U/r_T) \times 100$$

 r_U = peak area of each individual impurity from the *Sample solution* r_T = sum of all the peak areas from the *Sample solution***Acceptance criteria:** See *Table 3*.^{■1S} (USP36) Disregard any peak less than 0.05%.**Table 3**^{■1S} (USP36)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Orthocresol	0.85	0.5
Paracresol	0.99	0.5
Metacresol	1.00	—
Any unspecified impurity	—	0.1
Total impurities	—	1.0

SPECIFIC TESTS**• CLARITY OF SOLUTION****A.****Analysis:** Add 10 mL of Metacresol to 10 mL of hexane, and mix.**Acceptance criteria:** A clear solution is obtained.**B.****Analysis:** Add 1.0 mL of Metacresol to 20 mL of 1 N sodium hydroxide, and mix.**Acceptance criteria:** A clear solution is obtained.

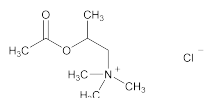
ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Add the following:

- **USP REFERENCE STANDARDS** (11)

USP Metacresol RS
USP Phenol RS
Phenol.
 C_6H_6O 94.11 ■^{1S} (USP36)

Methacholine Chloride

$C_8H_{18}ClNO_2$ 195.69
1-Propanaminium, 2-(acetyloxy)-*N,N,N*-trimethyl-, chloride, (±)-;
(±)-(2-Hydroxypropyl)trimethylammonium chloride acetate [62-51-1].

DEFINITION**Change to read:**

Methacholine Chloride ■^{1S} (USP36) contains NLT 98.0% and NMT 101.0% of methacholine chloride ($C_8H_{18}ClNO_2$) ■, calculated on the dried basis. ■^{1S} (USP36)

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197M)
- **B. IDENTIFICATION TESTS—GENERAL, Chloride** (191)
Sample solution: 20 mg/mL
Acceptance criteria: Meets the requirements

Add the following:

- **C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■^{1S} (USP36)

ASSAY**Change to read:**

- **PROCEDURE**

■ **Mobile phase:** 0.5 g/L of methanesulfonic acid in water
■ **Standard solution:** 50 µg/mL of USP Methacholine Chloride RS in water
■ **System suitability solution:** 10 µg/mL of USP Acetylcholine Chloride RS in *Standard solution*
■ **Sample solution:** 50 µg/mL of Methacholine Chloride in water

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: IC

Detector: Conductivity

Columns

Guard: 4.0-mm x 50-mm; L77¹ packing

Analytical: 4.0-mm x 25-cm; L77¹ packing

Suppressor: Ion-exchange membrane autosuppressor² or a suitable chemical suppression system

Suppressant: Autosuppression

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 2 between acetylcholine and methacholine, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methacholine chloride ($C_8H_{18}ClNO_2$) in the portion of Methacholine Chloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Methacholine Chloride RS in the *Standard solution* (µg/mL)

C_U = concentration of Methacholine Chloride in the *Sample solution* (µg/mL) ■^{1S} (USP36)

Acceptance criteria: 98.0%–101.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%
- **HEAVY METALS, Method II** (231): NMT 20 ppm

Delete the following:

- **ACETYLCHOLINE CHLORIDE**

Sample solution: 100 mg/mL

Analysis: To 2 mL of *Sample solution* add 3 mL of 200 mg/mL solution of sodium perchlorate, shake, and immerse in ice water for 5 min.

Acceptance criteria: No precipitate is formed. ■^{1S} (USP36)

Add the following:

- **ORGANIC IMPURITIES**

Mobile phase: 0.5 g/L of methanesulfonic acid in water

System suitability solution: 1 mg/mL of USP

Methacholine Chloride RS and 1 µg/mL of USP Acetylcholine Chloride RS in water

Standard solution: 1 µg/mL of USP Methacholine Chloride RS in water

Sample solution: 1 mg/mL of Methacholine Chloride in water

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: IC

Detector: Conductivity

Columns

Guard: 4.0-mm x 50-mm; L77¹ packing

Analytical: 4.0-mm x 25-cm; L77¹ packing

Suppressor: Ion-exchange membrane autosuppressor¹ or a suitable chemical suppression system

¹ Available as IonPac CS17.

² Available as Cation Self-Regenerating Suppressor (CSRS) from Dionex Inc., or equivalent.

Suppressant: Autosuppression

Flow rate: 1 mL/min

Injection volume: 20 μ L

Run time: Two times the retention time of methacholine

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 2 between acetylcholine and methacholine

Signal-to-noise ratio: NLT 2 for acetylcholine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of beta-methylcholine or acetylcholine in the portion of Methacholine Chloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of beta-methylcholine or acetylcholine from the *Sample solution*

r_S = peak response of methacholine chloride from the *Standard solution*

C_S = concentration of USP Methacholine Chloride RS in the *Standard solution* (μ g/mL)

C_U = concentration of Methacholine Chloride in the *Sample solution* (μ g/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Beta-methylcholine ^a	0.6	0.10
Acetylcholine	0.8	0.10
Methacholine	1.0	—

^a 2-Hydroxy-N,N,N-trimethylpropan-1-aminium chloride.

■1S (USP36)

SPECIFIC TESTS

• LOSS ON DRYING (731)

Analysis: Dry a sample at 105° for 4 h.

Acceptance criteria: NMT 1.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Add the following:

■ USP REFERENCE STANDARDS (11)

USP Acetylcholine Chloride RS

USP Methacholine Chloride RS ■1S (USP36)

Methenamine Mandelate Delayed-Release Tablets

DEFINITION

Methenamine Mandelate Delayed-Release Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of methenamine mandelate ($C_6H_{12}N_4 \cdot C_8H_8O_3$).

IDENTIFICATION

Add the following:

■ A. INFRARED ABSORPTION (197K)

Sample: Triturate an equivalent to 5.0 mg of methenamine mandelate from finely powdered Tablets with 5 mL of chloroform, and pass through a filter of 0.45- μ m pore size. Evaporate the solvent, and allow the residue to air-dry.

Acceptance criteria: Meet the requirements ■1S (USP36)

ASSAY

• PROCEDURE

Sample solution: Transfer an equivalent to 60 mg of methenamine mandelate, from finely powdered Tablets (NLT 20), to a 250-mL conical flask. Add 15 mL of dehydrated alcohol, stir to dissolve, and add 40 mL of chloroform.

Titrimetric system

Mode: Direct titration

Titrant: 0.05 N silver nitrate in dehydrated alcohol prepared as follows. Dissolve by stirring 8.5 g of silver nitrate in 1000 mL of dehydrated alcohol. Transfer 100 mg of sodium chloride, previously dried at 110° for 2 h, to a 100-mL beaker, and dissolve in 50 mL of water. Titrate with the silver nitrate solution to the potentiometric endpoint, using a silver billet indicator electrode and a silver-silver chloride double-junction reference electrode containing a potassium nitrate salt bridge. Calculate the normality of the titrant.

Endpoint detection: Potentiometric

Analysis: Titrate the *Sample solution* with *Titrant*, determining the endpoint potentiometrically, using a silver billet indicator electrode and a silver-silver chloride double-junction reference electrode containing a potassium nitrate salt bridge. Each mL of 0.05 N silver nitrate is equivalent to 7.308 mg of methenamine mandelate ($C_6H_{12}N_4 \cdot C_8H_8O_3$).

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

- **DISINTEGRATION (701):** 2.5 h, determined as directed in *Delayed-Release (Enteric-Coated) Tablets*
- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

SPECIFIC TESTS

Delete the following:

- **OTHER REQUIREMENTS** Delayed-release Tablets respond to the *Identification* test and meet the requirements for *Uniformity of dosage units* and *Assay* under *Methenamine Mandelate Tablets*. ■1S (USP36)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.
- **USP REFERENCE STANDARDS (11)**
USP Methenamine Mandelate RS

Metoprolol Succinate Extended-Release Tablets

DEFINITION

Metoprolol Succinate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$.

IDENTIFICATION

A. INFRARED ABSORPTION (197K)

Sample solution: Equivalent to 200 mg of metoprolol succinate from 1 or more Tablets to a stoppered centrifuge tube. Add 40 mL of pH 6.8 Phosphate Buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*) and 40 mL of methylene chloride, and shake for 5 min. Centrifuge, filter, and use the aqueous phase as the *Sample solution*.

Sample: Transfer 3 mL of the *Sample solution* to a separator. Add 2 mL of ammonium hydroxide, and extract with 20 mL of methylene chloride. Filter the methylene chloride phase. Grind 1 mL of the filtrate with 300 mg of potassium bromide, dry in a current of warm air, and prepare a disk.

Acceptance criteria: The IR spectrum of the *Sample* exhibits maxima only at the same wavelengths as that obtained from a similar preparation of USP Metoprolol Succinate RS (presence of metoprolol).

B. INFRARED ABSORPTION (197K)

Sample: Transfer 5 mL of the *Sample solution* prepared in *Identification test A* into a glass-stoppered test tube. Add 2 mL of 5 N hydrochloric acid, and extract with 5 mL of ether. Filter the ether phase. Grind 2 mL of the filtrate with 300 mg of potassium bromide, dry in a current of warm air, and prepare a disk.

Acceptance criteria: The IR spectrum of the *Sample* exhibits maxima only at the same wavelengths as that obtained from a similar preparation of succinic acid (presence of succinate).

ASSAY

PROCEDURE

Analysis: Determine the mean percentage value of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ from the Tablets analyzed in the test for *Uniformity of Dosage Units* (905).

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

DISSOLUTION (711)

Test 1 (RB 1-Aug-2012)

Medium: pH 6.8 Phosphate Buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, and 20 h

Buffer, Mobile phase, and Standard solution: Proceed as directed in the test for *Uniformity of Dosage Units* (905).

Analysis: Proceed as directed in the test for *Uniformity of Dosage Units* (905), except use 5.0 mL of a filtered portion of the solution under test as the *Sample solution*, and use *Medium* as the blank, in comparison with a *Standard solution* having a known concentration of USP Metoprolol Succinate RS in the same *Medium*.

Acceptance criteria: See Table 1. (RB 1-Aug-2012)

Table 1

Time (h)	Amount Dissolved (%)
1	NMT 25
4	20–40
8	40–60
20	NLT 80

The percentages of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* (711).

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Simulated gastric fluid without enzyme, pH 1.2; 500 mL

Apparatus 2: 75 rpm

Time: 1, 4, 8, and 20 h

Buffer: 1 M monobasic sodium phosphate, 1 M phosphoric acid, and water (50:8:942). If necessary, adjust with 1 M monobasic sodium phosphate or 1 M phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (250:750)

Standard solution: Prepare a solution of USP Metoprolol Succinate RS in *Medium* as directed in *Table 2*.

Table 2

Tablet Strength (mg as metoprolol succinate)	Concentration (mg/mL)
200	0.380
100	0.190
50	0.095
25	0.048

Sample solution: Pass the solution under test through a suitable filter.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm; 4-μm packing L7

Flow rate: 1 mL/min

Injection volume: See *Table 3*.

Table 3

Tablet Strength (mg as metoprolol succinate)	Volume (μL)
25	40
50	20
100	10
200	5

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1500 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis:

Samples: *Standard solution* and *Sample solution*
Calculate the concentration, C_i , in mg/mL, of metoprolol succinate dissolved in *Medium* at each time point, i :

$$\text{Result} = (r_U/r_S) \times C_S$$

r_U = peak response of metoprolol from the *Sample solution*

r_S = peak response of metoprolol from the *Standard solution*

C_S = concentration of USP Metoprolol Succinate RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ dissolved (Q_i), at each time point i :

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_3)] + [C_1 \times V_3]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - (2 \times V_3))] + [(C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times (V - (3 \times V_3))] + [(C_3 + C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

C_i = concentration of metoprolol succinate in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*; 500 mL

V_3 = volume of the *Sample solution* withdrawn from the *Medium* (mL)

L = label claim (mg/Tablet)

Tolerances: See Table 4.

Table 4

Time Point (i)	Time (hr)	Amount Dissolved (%)
1	1	NMT 20
2	4	20–40
3	8	55–85
4	20	NLT 80

The percentages of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ dissolved at the times specified conform to *Acceptance Table 2* in *Disso-*

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

Procedure for content uniformity

Buffer: Mix 50 mL of 1 M monobasic sodium phosphate and 8.0 mL of 1 M phosphoric acid, and dilute with water to 1000 mL. If necessary, adjust with 1 M monobasic potassium phosphate or 1 M phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (250:750)

Standard solution: 0.05 mg/mL of USP Metoprolol Succinate RS in *Mobile phase*

Sample stock solution: Nominally 1 mg/mL of metoprolol succinate prepared as follows. Transfer 1 Tablet to a suitable volumetric flask, add about 5 mL of water, and allow the Tablet to disintegrate. Add a volume of alcohol to fill 30% of final volume, and shake for 30 min. Add a portion of 0.1 N hydrochloric acid to fill 50% of the flask volume, and shake for an additional 30 min. Dilute with 0.1 N hydrochloric acid to volume. Filter, and discard the first 10 mL of the filtrate.

Sample solution: Nominally 0.05 mg/mL of metoprolol succinate from the *Sample stock solution* in *Mobile phase*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4-mm \times 12.5-cm; packing L7

Flow rate: 1 mL/min

Injection volume: 40 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ in the Tablet taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of metoprolol from the *Sample solution*

r_S = peak response of metoprolol from the *Standard solution*

C_S = concentration of USP Metoprolol Succinate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of metoprolol succinate in the *Sample solution* (mg/mL)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

Change to read:

- **LABELING:** Label it to indicate the content of metoprolol succinate and its equivalent, expressed as metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$. • When more than one *Disso-*

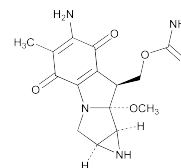
lution test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. • (RB 1-Aug-2012)

- **USP REFERENCE STANDARDS (11)**

USP Metoprolol Succinate RS

Mitomycin

Change to read:



$C_{15}H_{18}N_4O_5$ 334.33
Azirino[2',3':3,4]pyrrolo[1,2-*a*]indole-4,7-dione, 6-amino-8-[[aminocarbonyloxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1a \rightarrow 1'S]-(1 α ,8 β ,8a α ,8b α)]-; (1a S ,8 S ,8a R ,8b S)-(6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2',3':3,4]pyrrolo[1,2-*a*]indol-8-yl)methyl carbamate; (USP36)
Mitomycin C [50-07-7].

DEFINITION

Mitomycin has a potency of NLT 970 μ g/mg of mitomycin ($C_{15}H_{18}N_4O_5$).

IDENTIFICATION• **A. INFRARED ABSORPTION** <197M>

Analysis: Do not dry the sample and standard.

Acceptance criteria: Meets the requirements

Change to read:

- **B.** ■The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*. ■1S (USP36)

ASSAY**Change to read:**• **PROCEDURE**

Mobile phase: Dissolve 1.54 g of ammonium acetate in 250 mL of methanol. Add 5.0 mL of 0.83 N acetic acid and water to make 1000 mL.

System suitability solution: 0.5 mg/mL of USP Mitomycin RS and 7.5 mg/mL of 3-ethoxy-4-hydroxybenzaldehyde in *N,N*-dimethylacetamide

Standard solution: 0.5 mg/mL of USP Mitomycin RS in *N,N*-dimethylacetamide

Sample solution: 0.5 mg/mL of Mitomycin in *N,N*-dimethylacetamide

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 365 nm

Column: ■3.9-mm ■1S (USP36) × 30-cm; ■10-μm ■1S (USP36) packing L11

Flow rate: 2 mL/min

Injection volume: 10 μL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for mitomycin and 3-ethoxy-4-hydroxybenzaldehyde are 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 1.8 between mitomycin and 3-ethoxy-4-hydroxybenzaldehyde, *System suitability solution*

Tailing factor: NMT 1.3, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in μg/mg, of mitomycin (C₁₅H₁₈N₄O₅) in the portion of Mitomycin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Mitomycin RS in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

P = potency of mitomycin in USP Mitomycin RS (μg/mg)

Acceptance criteria: NLT 970 μg/mg

SPECIFIC TESTS• **CRYSTALLINITY** <695>: Meets the requirements• **PH** <791>

Sample: 5-mg/mL suspension in water

Acceptance criteria: 6.0–7.5

• **WATER DETERMINATION, Method I** <921>: NMT 2.5%• **STERILITY TESTS** <71>: Where the label states that Mitomycin is sterile, it meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*.

- **BACTERIAL ENDOTOXINS TEST** <85>: Where the label states that Mitomycin is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 10.0 USP Endotoxin Units/mg of mitomycin.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

- **LABELING:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP REFERENCE STANDARDS** <11>

USP Endotoxin RS

USP Mitomycin RS

Mitomycin for Injection**DEFINITION**

Mitomycin for Injection contains NLT 90.0% and NMT 120.0% of the labeled amount of mitomycin (C₁₅H₁₈N₄O₅).

IDENTIFICATION**Delete the following:**■ **A. THIN-LAYER CHROMATOGRAPHY**

Standard solution: 1 mg/mL of USP Mitomycin RS

Sample solution: Nominally 1 mg/mL of mitomycin

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Adsorbent: 0.25-mm layer of chromatographic silica gel

Application volume: 2 μL

Developing solvent system: Butyl alcohol, glacial acetic acid, and water (4:2:1)

Spray reagent: 10 mg/mL of ninhydrin in alcohol

Analysis

Samples: *Standard solution* and *Sample solution*

Apply the *Standard solution* and the *Sample solution* to the plate. Allow the spots to dry, and develop the chromatograms in the *Developing solvent system*. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Spray the plate with *Spray reagent*. Heat the plate in an oven at 110° for 15 min. Mitomycin appears as a pink spot.

Acceptance criteria: The R_f value of the principal spot from the *Sample solution* corresponds to that of the *Standard solution*. ■1S (USP36)

Add the following:

- **A.** The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*. ■1S (USP36)

ASSAY**Change to read:**• **PROCEDURE**

Mobile phase: Dissolve 1.54 g of ammonium acetate in 250 mL of methanol. Add 5.0 mL of 0.83 N acetic acid and water to make 1000 mL.

System suitability solution: 0.5 mg/mL of USP Mitomycin RS and 7.5 mg/mL of 3-ethoxy-4-hydroxybenzaldehyde in *N,N*-dimethylacetamide

Standard solution: 0.5 mg/mL of USP Mitomycin RS in *N,N*-dimethylacetamide

Sample solution: Add an accurately measured volume of *N,N*-dimethylacetamide to 1 container of Mitomycin for Injection to obtain a solution that is nominally 0.5 mg/mL of mitomycin.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 365 nm

Column: ■3.9-mm-■15 (USP36) × 30-cm; ■10-μm-■15 (USP36) packing L11

Flow rate: 2 mL/min

Injection volume: 10 μL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for mitomycin and 3-ethoxy-4-hydroxybenzaldehyde are 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 1.8 between mitomycin and 3-ethoxy-4-hydroxybenzaldehyde, *System suitability solution*

Tailing factor: NMT 1.3, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of mitomycin (C₁₅H₁₈N₄O₅) in the container of Mitomycin for Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Mitomycin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of mitomycin in the *Sample solution* (mg/mL)

P = potency of mitomycin in USP Mitomycin RS (μg/mg)

F = conversion factor, 0.001 mg/μg

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

- **UNIFORMITY OF DOSAGE UNITS** (905): Meets the requirements

SPECIFIC TESTS

- **pH** (791)

Sample solution: Constitute as directed in the labeling.

Acceptance criteria: 6.0–8.0 where it contains mannitol, and 5.5–8.5 where it contains hydroxypropyl betadex

- **WATER DETERMINATION, Method Ia** (921)

Sample solution: Prepare as directed for a hygroscopic specimen, using the pooled contents of five containers.

Acceptance criteria: NMT 5.0%

- **BACTERIAL ENDOTOXINS TEST** (85): Contains NMT 10.0 USP Endotoxin Units/mg of mitomycin
- **STERILITY TESTS** (71): Meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*
- **CONSTITUTED SOLUTION:** At the time of use, it meets the requirements for *Injections* (1), *Constituted Solutions*.
- **OTHER REQUIREMENTS:** Meets the requirements in *Injections* (1)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve as described in *Injections* (1), *Containers for Sterile Solids*, protected from light. Store at 25°, excursions permitted between 15° and 30°.

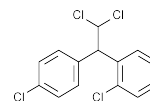
• USP REFERENCE STANDARDS (11)

USP Endotoxin RS

USP Mitomycin RS

Mitotane

Change to read:



C₁₄H₁₀Cl₄ 320.04

Benzene, 1-chloro-2-[2,2-dichloro-1-(4-chlorophenyl)ethyl]-,

■(RS)-;■1S (USP36)

(±)-1,1-Dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane [53-19-0].

DEFINITION

Change to read:

Mitotane contains NLT 97.0% and NMT 103.0% of mitotane (C₁₄H₁₀Cl₄), calculated on the ■anhydrous■1S (USP36) basis.

[CAUTION—Handle Mitotane with exceptional care, because it is a highly potent agent.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197M)

Delete the following:

- **B. ULTRAVIOLET ABSORPTION** (197U)

Sample solution: 200 μg/mL in methanol

Acceptance criteria: Meet the requirements■1S (USP36)

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.■1S (USP36)

ASSAY

Change to read:

- **PROCEDURE**

■Buffer: 1.38 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (75:25)

System suitability solution: 0.2 mg/mL of USP Mitotane RS and 0.2 mg/mL of the *p,p'*-isomer of mitotane in *Mobile phase*. [NOTE—The *p,p'*-isomer of mitotane is 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane known as *p,p'*-DDD.]

Standard solution: 0.2 mg/mL of USP Mitotane RS in *Mobile phase*

Sample solution: 0.2 mg/mL of Mitotane in *Mobile phase*. [NOTE—Inject within 48 h of preparation.]

Chromatographic system(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 230 nm**Column:** 4.6-mm × 25-cm; 5-μm packing L1**Flow rate:** 1 mL/min**Injection volume:** 10 μL**System suitability****Samples:** *System suitability solution* and *Standard solution*[NOTE—The relative retention times for the *p,p'*-isomer of mitotane and mitotane are about 0.92 and 1.0, respectively.]**Suitability requirements****Resolution:** NLT 1.5 between the *p,p'*-isomer of mitotane and mitotane, *System suitability solution***Tailing factor:** NMT 1.5, *Standard solution***Relative standard deviation:** NMT 1.0%, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of mitotane (C₁₄H₁₀Cl₄) in the portion of Mitotane taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response from the *Sample solution* r_S = peak response from the *Standard solution* C_S = concentration of USP Mitotane RS in the *Standard solution* (mg/mL) C_U = concentration of Mitotane in the *Sample solution* (mg/mL)**Acceptance criteria:** 97.0%–103.0% on the anhydrous basis ■1S (USP36)**IMPURITIES**

- **RESIDUE ON IGNITION** <281>: NMT 0.5%

SPECIFIC TESTS**Delete the following:**

- **MELTING RANGE OR TEMPERATURE** <741>: 75°–81° ■1S (USP36)

Delete the following:

- **LOSS ON DRYING** <731>:
Analysis: Dry in a vacuum at 60° for 2 h
Acceptance criteria: NMT 0.5% ■1S (USP36)

Add the following:

- **WATER DETERMINATION, Method Ia** <921>: NMT 0.5% ■1S (USP36)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.
- **USP REFERENCE STANDARDS** <11>
USP Mitotane RS

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** <197U>

Standard solution and Sample solution: Use the *Standard solution* and *Sample solution* as prepared in the *Dissolution* test.**Acceptance criteria:** The UV absorption spectra of the *Standard solution* and *Sample solution* exhibit maxima and minima at the same wavelength within ±3 nm.

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Phosphoric acid solution: Phosphoric acid and water (3:50)**Triethylamine solution:** Transfer 3 mL of triethylamine to 1000 mL of water. Adjust with *Phosphoric acid solution* to a pH of 5.3.**Mobile phase:** Acetonitrile and *Triethylamine solution* (11:9)**Standard solution:** 0.125 mg/mL of USP Mycophenolate Mofetil RS in acetonitrile**Sample solution:** Open Capsules, equivalent to 1.25 g of mycophenolate mofetil based on the label claim, and transfer the contents including Capsule shells into a 500-mL volumetric flask. Add 50 mL of water, and shake mechanically for a minimum of 15 min. Add 350 mL of acetonitrile, sonicate for 15 min, and shake mechanically for 20 min. Dilute with acetonitrile to volume. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, and dilute with acetonitrile to volume. Pass through a nylon filter of 0.45-μm pore size, and discard the first 5 mL of the filtrate.**Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 250 nm**Column:** 4.6-mm × 25-cm; 5-μm packing L7**Temperatures****Column:** 45°**Autosampler:** 10 ± 5°**Flow rate:** 1.5 mL/min**Injection volume:** 20 μL**System suitability****Sample:** *Standard solution***Suitability requirements****Tailing factor:** NMT 2**Relative standard deviation:** NMT 2.0%**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of the labeled amount of mycophenolate mofetil (C₂₃H₃₁NO₇) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response from the *Sample solution* r_S = peak response from the *Standard solution* C_S = concentration of mycophenolate mofetil in the *Standard solution* (mg/mL) C_U = nominal concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)**Mycophenolate Mofetil Capsules****DEFINITION**Mycophenolate Mofetil Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of mycophenolate mofetil (C₂₃H₃₁NO₇).

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION <711>

• Test 1 • (RB 1-Aug-2012)

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 40 rpm, with sinkers

Time: 20 min

Standard solution: 0.278 mg/mL of USP Mycophenolate Mofetil RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Detector: UV 250 nm

Path length: 0.1 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of mycophenolate mofetil ($C_{23}H_{31}NO_7$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of mycophenolate mofetil ($C_{23}H_{31}NO_7$) is dissolved.

• Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 40 rpm, with sinker

Time: 30 min

Standard solution: 0.028 mg/mL of USP Mycophenolate Mofetil RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable nylon filter of 0.45-μm pore size. Discard the first 3–5 mL, and dilute 1 mL of the filtrate with *Medium* to 10 mL.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV

Analytical wavelength: 250 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of mycophenolate mofetil ($C_{23}H_{31}NO_7$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

D = dilution factor, 10

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of mycophenolate mofetil ($C_{23}H_{31}NO_7$) is dissolved. • (RB 1-

Aug-2012)

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

• LIMIT OF DEGRADATION PRODUCTS

Mobile phase, Standard solution, Sample solution, and Chromatographic system: Proceed as directed in the *Assay*.

Sensitivity solution: 0.0625 μg/mL of USP Mycophenolate Mofetil RS in acetonitrile

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Tailing factor: NMT 2, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

[NOTE—The run time for the *Sample solution* is three times that of the retention time of the mycophenolate mofetil peak.]

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of mycophenolate mofetil from the *Standard solution*

C_S = concentration of USP Mycophenolate Mofetil RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)

F = relative response factor for each individual impurity (see *Table 1*)

Acceptance criteria: See *Table 1*.

Disregard peaks at relative retention times of 1.45 and 2.15. Disregard any peaks less than 0.05%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Mycophenolic acid ^a	0.6	1.4	1.0
Mycophenolate N-oxide analog ^b	0.8	1.0	0.2
Mycophenolate mofetil	1.0	—	—
Any single unspecified impurity	—	1.0	0.1
Total degradation products	—	—	1.5

^a (E)-6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuran-4-yl)-4-methyl-4-hexenoic acid.

^b 2-Morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuran-4-yl)-4-methyl-4-hexenoate N-oxide.

• LIMIT OF Z-MYCOPHENOLATE MOFETIL

[NOTE—Z-Mycophenolate mofetil is 2-morpholinoethyl (Z)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-5-phthalanyl)-4-methyl-4-hexenoate.]

Triethylamine solution: Proceed as directed in the *Assay*.

Mobile phase: Acetonitrile and *Triethylamine solution* (7:13)

Standard solution: 0.025 mg/mL of USP Mycophenolate Mofetil RS in acetonitrile

Sensitivity solution: 1.25 μg/mL of USP Mycophenolate Mofetil RS in acetonitrile

Sample solution: Open Capsules, equivalent to 1.25 g of mycophenolate mofetil based on the label claim, and transfer the contents including Capsule shells into a 500-mL volumetric flask. Add 50 mL of water, and shake mechanically for a minimum of 15 min. Add 350 mL of acetonitrile, sonicate for 15 min, and shake mechanically for 20 min. Dilute with acetonitrile to volume. Pass through a nylon filter of 0.45-μm pore size, and discard the first 2 mL of the filtrate.

Chromatographic system(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 215 nm**Column:** 4.6-mm × 15-cm; 3.5-μm packing L7**Column temperature:** 60°**Flow rate:** 1.5 mL/min**Injection volume:** 10 μL**Run time:** 1.7 times the retention time of the mycophenolate mofetil peak**System suitability****Samples:** *Standard solution* and *Sensitivity solution*

[NOTE—The relative retention times for mycophenolate mofetil and Z-mycophenolate mofetil are 1.0 and 1.1, respectively.]

Suitability requirements**Signal-to-noise ratio:** NLT 10, *Sensitivity solution***Tailing factor:** NMT 2.0, *Standard solution***Relative standard deviation:** NMT 5.0%, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of Z-mycophenolate mofetil in the portion of Capsules taken:

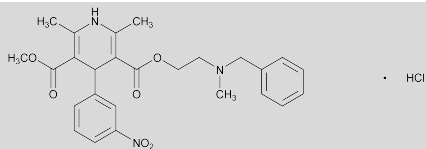
$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response of Z-mycophenolate mofetil from the *Sample solution* r_S = peak response of mycophenolate mofetil from the *Standard solution* C_S = concentration of USP Mycophenolate Mofetil RS in the *Standard solution* (mg/mL) C_U = nominal concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)**Acceptance criteria****Z-Mycophenolate mofetil:** NMT 0.10%**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in well-closed and light-resistant containers, and store at controlled room temperature.

Add the following:

- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- (RB 1-Aug-2012)
- **USP REFERENCE STANDARDS** <11>
USP Mycophenolate Mofetil RS

Add the following:**Nicardipine Hydrochloride** $C_{26}H_{29}N_3O_6 \cdot HCl$ 515.99

3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 2-[methyl(phenylmethyl)amino]ethyl ester, monohydrochloride;
2-(Benzylmethylamino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride [54527-84-3].

Nicardipine free base $C_{26}H_{29}N_3O_6$ 479.52
[55985-32-5].**DEFINITION**Nicardipine Hydrochloride contains NLT 98.0% and NMT 101.0% of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$), calculated on the dried basis.**IDENTIFICATION**

- **A. INFRARED ABSORPTION** <197K>

- **B. ULTRAVIOLET ABSORPTION** <197U>

Analytical wavelength: 355 nm**Sample solution:** 0.5 mg/mL in alcohol**Acceptance criteria:** The sample exhibits absorption maximum at 355 nm.

- **C. IDENTIFICATION TESTS—GENERAL, Chloride** <191>

Sample solution: 2.5 mg/mL in methanol**Acceptance criteria:** Meets the requirements**ASSAY**

- **PROCEDURE**

Sample: 300 mg of Nicardipine Hydrochloride**Titrimetric system**(See *Titrimetry* <541>.)**Mode:** Direct titration**Titrant:** 0.1 N perchloric acid VS**Endpoint detection:** Potentiometric**Blank:** 50 mL of glacial acetic acid and 10 mL of mercuric acetate TS**Analysis:** Dissolve the sample in 50 mL of glacial acetic acid and 10 mL mercuric acetate TS, by warming slightly, if necessary. Allow to cool, titrate with 0.1 N perchloric acid VS, and determine the end point potentiometrically. Perform a blank determination, and make any necessary corrections.Calculate the percentage of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$) in the portion of the sample taken:

$$\text{Result} = [(V_S/V_B) \times N \times F \times 100]/W$$

 V_S = Titrant volume consumed by the *Sample* (mL) V_B = Titrant volume consumed by the *Blank* (mL) N = normality of the *Titrant* (mEq/mL) F = equivalency factor, 51.57 mg/mEq W = sample weight (mg)**Acceptance criteria:** 98.0%–101.0% on the dried basis**IMPURITIES**

- **RESIDUE ON IGNITION** <281>: NMT 0.1%

- **HEAVY METALS, Method II** <231>: NMT 20 ppm

- **ORGANIC IMPURITIES**

[NOTE—Protect all solutions from light.]

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust the solution with potassium hydroxide to a pH of 4.8.**Solution A:** Acetonitrile and methanol (82:18)**Mobile phase:** *Solution A* and *Buffer* (40:60)**System suitability solution:** 0.6 mg/mL of USP Nicardipine Hydrochloride RS in the *Mobile phase* prepared as follows. To a suitable amount of USP Nicardipine Hydrochloride RS in a suitable volumetric flask, add the *Mobile phase* to fill about 10% of the volume of the flask, and sonicate for 2 min. Then add 10% hydrogen peroxide solution to fill an additional 10% of the volume of the flask. Allow it to stand for 30 min, then dilute with *Mobile phase* to volume. [NOTE—Nicardipine Hydrochloride degrades to produce nicardipine pyridine analog, nicardipine dimethyl ester analog, and nicardipine bis analog. Use a freshly prepared sample to avoid further degradation for analysis.]**Standard solution:** 3 μg/mL of USP Nicardipine Hydrochloride RS in *Mobile phase*

Sample solution: 0.6 mg/mL of Nicardipine Hydrochloride in *Mobile phase*. [NOTE—Sonication may be necessary for complete dissolution.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 237 nm

Column: 4.6-mm × 25-cm; 5-μm packing L7

Column temperature: 35°–40°. [NOTE—To attain resolution, the *Column temperature* may be adjusted instead of the *Mobile phase* composition.]

Flow rate: 1.5 mL/min

Injection volume: 50 μL

Run time: NLT four times the retention time of nicardipine

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between nicardipine and dimethylanalog and NLT 1.5 between bis analog and dimethyl analog, *System suitability solution*

Relative standard deviation: NMT 2%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of nicardipine in the *Standard solution*

C_S = concentration of USP Nicardipine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Nicardipine Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Nicardipine pyridine analog ^a	0.67	0.1
Nicardipine	1.00	—
Nicardipine dimethyl ester analog ^b	1.20	0.5
Nicardipine bis analog ^c	1.33	0.5
Any other individual unidentified impurity	—	0.1
Total impurities ^d	—	1.0

^a 3-[2-[Benzyl(methyl)amino]ethyl] 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate dihydrochloride.

^b Dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate.

^c Bis[2-[benzyl(methyl)amino]ethyl] 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate dihydrochloride.

^d Disregard peaks less than 0.01%.

SPECIFIC TESTS

• LOSS ON DRYING <731>

Analysis: Dry a sample at 105°, protected from light to constant weight.

Acceptance criteria: NMT 0.5%

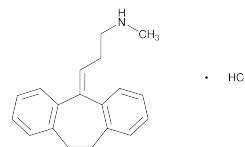
ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tightly closed containers, protected from light.

• USP REFERENCE STANDARDS <11>

USP Nicardipine Hydrochloride RS^{1S} (USP36)

Nortriptyline Hydrochloride



$C_{19}H_{21}N \cdot HCl$ 299.84

1-Propanamine, 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methyl-, hydrochloride; 10,11-Dihydro-N-methyl-5H-dibenzo[a,d]cycloheptene-Δ⁵. γ-propylamine hydrochloride [894-71-3].

DEFINITION

Nortriptyline Hydrochloride contains NLT 97.0% and NMT 101.5% of nortriptyline hydrochloride ($C_{19}H_{21}N \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A. ■INFRARED ABSORPTION <197K>**^{1S} (USP36)

Change to read:

- **B. ■**The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.^{1S} (USP36)
- **C. IDENTIFICATION TESTS—GENERAL, Chloride <191>**: Meets the requirements when tested as specified for alkaloidal hydrochlorides

ASSAY

Change to read:

• PROCEDURE

■**Solution A:** Phosphoric acid and water (1:10)

Buffer: Dissolve 1.4 g of dibasic sodium phosphate in 1 L of water, and adjust with *Solution A* to a pH of 7.7.

Mobile phase: Methanol and *Buffer* (70:30)

Standard solution: 0.2 mg/mL of USP Nortriptyline Hydrochloride RS in *Mobile phase*

Sample solution: 0.2 mg/mL of Nortriptyline Hydrochloride in *Mobile phase*

Chromatographic system(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 215 nm**Column:** 4.6-mm × 25-cm; 5-μm packing L7**Column temperature:** 45°**Flow rate:** 1.5 mL/min**Injection volume:** 10 μL**Run time:** 1.3 times the retention time of nortriptyline**System suitability****Sample:** *Standard solution***Suitability requirements****Tailing factor:** NMT 2.0**Relative standard deviation:** NMT 2.0%**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of nortriptyline hydrochloride (C₁₉H₂₁N · HCl) in the portion of the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response from the *Sample solution* r_S = peak response from the *Standard solution* C_S = concentration of USP Nortriptyline Hydrochloride RS in the *Standard solution* (mg/mL) C_U = concentration of Nortriptyline Hydrochloride in the *Sample solution* (mg/mL)**Acceptance criteria:** 97.0%–101.5% on the dried basis ■1S (USP36)**IMPURITIES**

- **RESIDUE ON IGNITION** <281>: NMT 0.1%
- **HEAVY METALS**, *Method II* <231>: NMT 10 ppm

Change to read:• **ORGANIC IMPURITIES**■ **Solution A:** 400 mg/mL of tetrabutylammonium hydroxide in water**Solution B:** Phosphoric acid and water (1:7)**Buffer:** Dissolve 0.7 g of potassium dihydrogen phosphate in 900 mL water. Add 3.25 mL of *Solution A*, and adjust with *Solution B* to a pH of 7.5. Dilute with water to 1 L.**Mobile phase:** Methanol and *Buffer* (75:25). [NOTE—The *Mobile phase* ratio can be adjusted to 70:30 to meet the system suitability requirements.]**System suitability solution:** 2.0 μg/mL each of USP Amitriptyline Related Compound B RS, USPCyclobenzaprine Related Compound B RS, and USP Nortriptyline Hydrochloride RS in *Mobile phase***Standard solution:** 2.0 μg/mL of USP Nortriptyline Hydrochloride RS in *Mobile phase***Sample solution:** 2.0 mg/mL of Nortriptyline Hydrochloride in *Mobile phase***Chromatographic system**(See *Chromatography* <621>, *System Suitability*.)**Mode:** LC**Detector:** UV 220 nm**Column:** 4.6-mm × 15-cm; 5-μm packing L7**Column temperature:** 35°. [NOTE—The *Column temperature* can be adjusted to 45° to meet the system suitability requirements.]**Flow rate:** 1 mL/min**Injection volume:** 10 μL**Run time:** 3 times the retention time of nortriptyline**System suitability****Samples:** *System suitability solution* and *Standard solution***Suitability requirements****Resolution:** NLT 1.4 between the amitriptyline related compound B and cyclobenzaprine related com-pound B peaks; NLT 2.0 between the cyclobenzaprine related compound B and nortriptyline peaks, *System suitability solution***Relative standard deviation:** NMT 5.0%, *Standard solution***Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Nortriptyline Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

 r_U = peak response of each individual impurity from the *Sample solution* r_S = peak response of nortriptyline from the *Standard solution* C_S = concentration of USP Nortriptyline Hydrochloride RS in the *Standard solution* (mg/mL) C_U = concentration of Nortriptyline Hydrochloride in the *Sample solution* (mg/mL) F = relative response factor (see *Table 1*)**Acceptance criteria:** See *Table 1*. Disregard peaks less than 0.05% of the area of the principal peak from the *Standard solution*.**Table 1**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amitriptyline related compound A ^a	0.5	1.0	0.05
Amitriptyline related compound B	0.8	0.58	0.15
Cyclobenzaprine related compound B	0.9	1.0	0.10
Nortriptyline	1.0	—	—
Any other individual impurity	—	1.0	0.10
Total impurities	—	—	0.2

^a Dibenzosuberone.

■1S (USP36)

SPECIFIC TESTS**Delete the following:**

- **MELTING RANGE OR TEMPERATURE**, *Class I* <741>: 215°–220°, but the range between beginning and end of melting does not exceed 3°. ■1S (USP36)
- **LOSS ON DRYING** <731>
Analysis: Dry a sample at 105° for 3 h.
Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

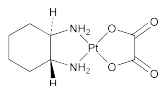
- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Change to read:• **USP REFERENCE STANDARDS** <11>

- USP Amitriptyline Related Compound B RS
5-[3-(Dimethylamino)propyl]-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ol.
C₂₀H₂₅NO 295.42

USP Cyclobenzaprine Related Compound B RS
 3-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-*N*-methyl-
 1-propanamine hydrochloride.
 $C_{19}H_{19}N \cdot HCl$ 297.81 \square 15 (USP36)
 USP Nortriptyline Hydrochloride RS

Oxaliplatin



$C_8H_{14}N_2O_4Pt$ 397.29
 [SP-4-2-(1*R*-trans)]-(1,2-Cyclohexanediamine-*N,N'*)
 [ethanedioato(2-)-*O,O'*]platinum;
cis-[(1*R*,2*R*)-1,2-Cyclohexanediamine-*N,N'*][oxalato(2-)-
O,O']platinum [61825-94-3].

DEFINITION

Oxaliplatin contains NLT 98.0% and NMT 102.0% of oxaliplatin ($C_8H_{14}N_2O_4Pt$), calculated on the dried basis.

[CAUTION]—Great care should be taken in handling Oxaliplatin, because it is a potentially cytotoxic agent.]

IDENTIFICATION

- A. INFRARED ABSORPTION** (197K)
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

PROCEDURE

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Polypropylene HPLC autosampler vials should be used.]

Buffer: Weigh 2.72 g of monobasic potassium phosphate (anhydrous) and 1.80 g of 1-pentanesulfonic acid sodium salt into a suitable container. Add 2000 mL of water, and mix well to completely dissolve all solids. Transfer 0.5 mL of triethylamine to the buffer solution, and mix thoroughly. Adjust the solution by dropwise addition of phosphoric acid to a pH of 4.30 ± 0.05 .

Mobile phase: Methanol and *Buffer* (3:17)

Oxaliplatin standard stock solution: 0.5 mg/mL of USP Oxaliplatin RS in water

Oxaliplatin related compound B standard stock solution: Transfer USP Oxaliplatin Related Compound B RS to a suitable volumetric flask, add 25% of the final volume of methanol, and sonicate for approximately 2 min to disperse the solids. Add approximately 65% of the final volume of 0.001 M nitric acid, and sonicate for an additional 30 min to dissolve the solids. Allow to cool if necessary. Dilute with 0.001 M nitric acid to volume, and mix to obtain a solution having a known concentration of 0.125 mg/mL. [NOTE—USP Oxaliplatin Related Compound B RS is converted to (SP-4-2)-diaqua [(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum during preparation of this solution.]

Oxaliplatin related compound C standard stock solution: 0.1 mg/mL of USP Oxaliplatin Related Compound C RS in water

System suitability solution: 2 mg/mL of Oxaliplatin in 0.005 M sodium hydroxide. Allow this solution to stand at room temperature for at least 5 days. Transfer 10 mL of this solution, 10 mL of *Oxaliplatin related compound B standard stock solution*, and 5 mL of *Oxaliplatin related compound C standard stock solution* into a 100-mL volumetric flask, and dilute with water to volume. [NOTE—The preparation of the *System suitability solution* forms diaquodiaminocyclohexaneplatinum dimer.]

Standard solution: 0.1 mg/mL of USP Oxaliplatin RS in water from *Oxaliplatin standard stock solution*

Sample solution: 0.1 mg/mL of Oxaliplatin in water

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Flow rate: 1 mL/min

Injection volume: 50 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times, measured with respect to oxaliplatin, of oxaliplatin related compound C, oxaliplatin related compound B, and diaquodiaminocyclohexaneplatinum dimer are 0.8, 2.7, and 6, respectively.]

Suitability requirements

Resolution: NLT 2.0 between oxaliplatin and oxaliplatin related compound C, *System suitability solution*

Tailing factor: Between 0.8 and 2.0 for oxaliplatin, *System suitability solution*

Relative standard deviation: NMT 2.0% for oxaliplatin, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
 Calculate the percentage of oxaliplatin ($C_8H_{14}N_2O_4Pt$) in the portion of Oxaliplatin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Oxaliplatin RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxaliplatin in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

LIMIT OF SILVER

Sample stock solution: Dissolve 100 mg of Oxaliplatin, weighed, in 50 mL of water to obtain a solution having a concentration of 2 mg/mL.

Sample solution: 1 mg/mL of Oxaliplatin in 0.5 M nitric acid from the *Sample stock solution*

Standard stock solution: Dilute a commercially available silver nitrate atomic absorption standard solution containing 1000 ppm of silver in 0.5 M nitric acid quantitatively, and stepwise if necessary, with 0.5 M nitric acid to obtain a 10-ppb solution.

Standard solution 1: Mix 20 μ L of the *Sample stock solution* and 8 μ L of the *Standard stock solution*, and dilute with 0.5 M nitric acid to 40 μ L.

Standard solution 2: Mix 20 μ L of the *Sample stock solution* and 16 μ L of the *Standard stock solution*, and dilute with 0.5 M nitric acid to 40 μ L.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: Atomic absorption spectrophotometer equipped with a silver hollow-cathode lamp and graphite furnace

Analytical wavelength: Silver emission line of 328.1 nm

Blank: 0.5 M nitric acid

Analysis

Samples: *Sample solution*, *Standard solution 1*, and *Standard solution 2*

Plot the absorbances of the *Sample solution*, *Standard solution 1*, and *Standard solution 2* versus their concentrations, in ppb, of silver, and draw the straight line best fitting the three plotted points. The intercept on

the x-axis of the extended regression line indicates the silver concentration in the *Sample solution*. Calculate the concentration of silver, in ppm, in the portion of Oxaliplatin taken:

$$\text{Result} = (C/W) \times 100$$

C = absolute value of the intercept, in ppb of silver, on the x-axis
 W = weight of Oxaliplatin taken for the preparation of the *Sample stock solution* (mg)

Acceptance criteria: NMT 5 ppm

• HEAVY METALS

Standard stock solution: Transfer 1 mL each of 1000-ppm standard solutions of cadmium, chromium, copper, iron, nickel, and lead (commercially available) to a 100-mL volumetric flask. Add 5 mL of nitric acid, and dilute with water to volume.

Internal standard solution: Transfer 1 mL of a 10,000-ppm standard solution of yttrium (commercially available) to a 100-mL volumetric flask, and dilute with 5% nitric acid to volume.

Standard solutions: Transfer 0.2, 2.0, and 20.0 mL of *Standard stock solution* to separate 100-mL volumetric flasks. Add 1.0 mL of *Internal standard solution* and 5.0 mL of nitric acid to each flask, and dilute with water to volume. The concentrations of these solutions are 0.02, 0.20, and 2.00 ppm, respectively.

Blank solution: Transfer 1.0 mL of *Internal standard solution* and 5.0 mL of nitric acid to a 100-mL volumetric flask, and dilute with water to volume.

Sample solution: Weigh 1 g of Oxaliplatin into a 100-mL volumetric flask, and add 80 mL of water. Stir vigorously for several min with a magnetic stirrer until no more sample seems to be dissolving. Add 5 mL of nitric acid, and mix again until the sample is completely dissolved. Remove the stirrer bar from the flask, rinsing it before removal. Add 1.0 mL of the *Internal standard solution*, and dilute with water to volume.

Instrumental conditions

(See *Plasma Spectrochemistry* (730).)

Measure the responses of the elements cadmium, chromium, copper, iron, nickel, lead, and yttrium (internal standard), using an inductively coupled plasma–atomic optical emission spectrometer (ICP–OES), by measuring the emissions at 226.502, 283.563, 327.395, 259.940, 221.648, 220.353, and 371.029 nm, respectively. Optimize the instrument settings as directed by the manufacturer.

System suitability

Before samples are analyzed, the instrument must pass a suitable performance check. Generate the calibration curve, using the *Blank solution* and the *Standard solutions*, and run these solutions in the following order: the *Blank solution*, then the 0.02-, 0.20-, and 2.00-ppm *Standard solutions*. The linear regression coefficient is NLT 0.99; the response of the *Blank solution* is between –5.0 and 5.0 ppb for each element; and the responses of yttrium obtained from the *Standard solutions* are drifted by NMT 5.0% of the response obtained from the *Blank solution*. Run the 0.20-ppm *Standard solution*, and record the responses of each element: the relative standard deviations for replicate runs are NMT 5.0%; and the recovery against the calibration curve is between 95% and 105%. After samples are analyzed, the instrument must pass the same suitable performance check to ensure that the calibration is still valid.

Analysis

Sample: *Sample solution*

Record the responses of each element, and determine the concentration of each element, using the calibration

graph. Calculate the content of total elements, in ppm, in the portion of Oxaliplatin taken:

$$\text{Result} = [(\sum C_i)/W] \times 100$$

C_i = concentration of each element in the *Sample solution* (ppm)

W = weight of Oxaliplatin taken to prepare the *Sample solution* (g)

Acceptance criteria: NMT 20 ppm

• CONTENT OF PLATINUM

Sample: Ignite an empty porcelain crucible fitted with a lid in a furnace at 800° for 30 min. Cool in a desiccator, and weigh. Add 200 mg of the Oxaliplatin, weighed, to the crucible, and ignite in a furnace by stepwise increments as follows. Introduce into the furnace, and increase the temperature to 200° within 15 min, then to 400° within 15 min, then to 600° within 15 min, then finally to 800° within 15 min. Allow to remain in the furnace at 800° for 30 min. Remove, cool in a desiccator, and reweigh. Calculate the percentage of platinum in the portion of Oxaliplatin taken:

$$\text{Result} = (W_2/W_1) \times 100$$

W_2 = weight of residue after ignition (mg)

W_1 = weight of oxaliplatin before ignition (mg)

Acceptance criteria: 48.1%–50.1% of the oxaliplatin taken, on the dried basis

• ORGANIC IMPURITIES, PROCEDURE 1: LIMIT OF OXALIC ACID

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Polypropylene HPLC autosampler vials should be used.]

Buffer: Add 1.36 g of potassium dihydrogen phosphate to 10 mL of 10% tetrabutylammonium hydroxide in water, and dilute with water to 1000 mL. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (1:4)

Standard stock solution: 0.06 mg/mL of USP Oxaliplatin Related Compound A RS in water

Standard solution: 15 µg/mL of USP Oxaliplatin Related Compound A RS in water from the *Standard stock solution*

System suitability solution: 0.05 mg/mL of sodium nitrate in water. Transfer 2 mL of this solution and 25 mL of the *Standard stock solution* to a 100-mL volumetric flask, and dilute with water to volume.

Sensitivity solution: 1.5 µg/mL of USP Oxaliplatin Related Compound A RS in water from the *Standard solution*

Sample solution: 2 mg/mL of Oxaliplatin in water

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*

[NOTE—The elution order is sodium nitrate, followed by oxalic acid.]

Suitability requirements

Resolution: NLT 2.0 between oxalic acid and sodium nitrate, *System suitability solution*

Relative standard deviation: NMT 3.0% for oxalic acid, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of oxalic acid in the portion of Oxaliplatin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of oxalic acid from the *Sample solution*

r_S = peak response of oxalic acid from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound A RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxaliplatin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of anhydrous oxalic acid, 90.03

M_{r2} = molecular weight of USP Oxaliplatin Related Compound A RS, 126.07

Acceptance criteria: NMT 0.1%

• **ORGANIC IMPURITIES, PROCEDURE 2: LIMIT OF (SP-4-2)-DIAQUA[(1R,2R)-CYCLOHEXANE-1,2-DIAMINE-*N,N'*]PLATINUM, OXALIPLATIN RELATED COMPOUND C, AND UNSPECIFIED IMPURITIES**

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Polypropylene HPLC autosampler vials should be used.]

Mobile phase, Oxaliplatin standard stock solution, Oxaliplatin related compound B standard stock solution, Oxaliplatin related compound C standard stock solution, System suitability solution, and Chromatographic system: Proceed as directed in the *Assay*.

Standard solution: 0.01 mg/mL of oxaliplatin, 0.01 mg/mL of oxaliplatin related compound B, and 0.004 mg/mL of oxaliplatin related compound C in water from *Oxaliplatin standard stock solution*, *Oxaliplatin related compound B standard stock solution*, and *Oxaliplatin related compound C standard stock solution*, respectively

Sample solution: 2 mg/mL of Oxaliplatin in water

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between oxaliplatin and oxaliplatin related compound C, *System suitability solution*

Tailing factor: Between 0.8 and 2.0 for oxaliplatin, *System suitability solution*

Relative standard deviation: NMT 3.0% for oxaliplatin, oxaliplatin related compound B, and oxaliplatin related compound C, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum in the portion of Oxaliplatin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum from the *Sample solution*

r_S = peak response of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound B RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxaliplatin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum, 345.30

M_{r2} = molecular weight of USP Oxaliplatin Related Compound B RS, 433.28

[NOTE—USP Oxaliplatin Related Compound B RS is converted to (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum in solution preparation.]

Calculate the percentage of oxaliplatin related compound C in the portion of Oxaliplatin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of oxaliplatin related compound C from the *Sample solution*

r_S = peak response of oxaliplatin related compound C from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound C RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxaliplatin in the *Sample solution* (mg/mL)

Calculate the percentage of diaquodiaminocyclohexaneplatinum dimer in the portion of Oxaliplatin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of diaquodiaminocyclohexaneplatinum dimer from the *Sample solution*

r_S = peak response of oxaliplatin related compound B from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound B RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxaliplatin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2-diamine-*N,N'*]platinum, 345.30

M_{r2} = molecular weight of USP Oxaliplatin Related Compound B RS, 433.28

F = relative response factor for diaquodiaminocyclohexaneplatinum dimer, measured with respect to USP Oxaliplatin Related Compound B RS, 2.5

Calculate the percentage of any other unspecified impurity in the portion of Oxaliplatin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of any other unspecified impurity from the *Sample solution*

r_S = peak response of oxaliplatin from the *Standard solution*

C_S = concentration of oxaliplatin in the *Standard solution* (mg/mL)

C_U = concentration of Oxaliplatin in the *Sample solution* (mg/mL)

Acceptance criteria: See Table 1.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxaliplatin related compound C	0.8	—	0.1
Oxaliplatin	1.0	—	—

^a Total impurities include oxalic acid (from *Procedure 1*) and all impurities from *Procedure 2*.

Table 1 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
(SP-4-2)-Diaqua [(1 <i>R</i> ,2 <i>R</i>)-cyclohexane-1,2-diamine- <i>N,N'</i>]platinum	2.7	—	0.1
Diaquodiaminocyclohexaneplatinum dimer	6	2.5	0.1
Any individual unspecified impurity	—	—	0.10
Total impurities ^a	—	—	0.30

^a Total impurities include oxalic acid (from Procedure 1) and all impurities from Procedure 2.

Change to read:

• ORGANIC IMPURITIES, PROCEDURE 3: LIMIT OF OXALIPLATIN RELATED COMPOUND D

[NOTE—Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the *Sample solution* within 20 min of preparation. Polypropylene HPLC autosampler vials should be used.]

Mobile phase: Methanol and ethanol (7:3)

Oxaliplatin related compound D standard stock solution: 0.05 mg/mL of USP Oxaliplatin Related Compound D RS in methanol

Oxaliplatin related compound D standard solution: 15 µg/mL of USP Oxaliplatin Related Compound D RS in methanol from *Oxaliplatin related compound D standard stock solution*

Oxaliplatin standard stock solution: 0.75 mg/mL of USP Oxaliplatin RS in methanol

Oxaliplatin standard solution: 37.5 µg/mL of USP Oxaliplatin RS in methanol from *Oxaliplatin standard stock solution*

■ Oxaliplatin blank solution: Transfer 40 mL of *Oxaliplatin standard stock solution* to a 50-mL volumetric flask, and dilute with methanol to volume. ^{15 (USP36)}

Standard solutions: Transfer 40 mL of *Oxaliplatin standard stock solution* to separate 50-mL volumetric flasks. Add 1.0, 3.0, and 5.0 mL of *Oxaliplatin related compound D standard solution* to each flask, and dilute with methanol to volume. The concentration of oxaliplatin in these solutions is 0.6 mg/mL. The concentrations of oxaliplatin related compound D in these solutions are 0.3, 0.9, and 1.5 µg/mL, respectively.

System suitability solution: Transfer 5.0 mL of *Oxaliplatin standard solution* and 4.0 mL of *Oxaliplatin related compound D standard stock solution* to a 50-mL volumetric flask, and dilute with methanol to volume.

Sample solution: Transfer 30 mg of Oxaliplatin into a 50-mL volumetric flask, and dilute with methanol to volume.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L70

Column temperature: 40°

Flow rate: 0.3 mL/min

Injection volume: 20 µL

Run time: 30 min

System suitability

Samples: 0.9-µg/mL *Standard solution* and *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between oxaliplatin and oxaliplatin related compound D, *System suitability solution*

Relative standard deviation: NMT 3.0% for the peak height ratio of oxaliplatin related compound D to the sum of oxaliplatin and oxaliplatin related compound D; 0.9-µg/mL *Standard solution*

Analysis

Samples: *Standard solutions* and *Sample solution*

■ Subtract the oxaliplatin related compound D peak height obtained in the *Oxaliplatin blank solution* from the oxaliplatin related compound D peak height obtained in the *Standard solutions*. [NOTE—USP Oxaliplatin RS may contain a small amount of oxaliplatin related compound D.] Plot a calibration curve for the *Standard solutions* with the peak height ratios of oxaliplatin related compound D to the sum of oxaliplatin and oxaliplatin related compound D on the y-axis and the concentration ratios of oxaliplatin related compound D, in µg/mL, to the sum of oxaliplatin and oxaliplatin related compound D concentrations, in mg/mL, on the x-axis. Read the concentration ratio of oxaliplatin related compound D, in µg/mL, to the sum of oxaliplatin and oxaliplatin related compound D, in mg/mL, in the *Sample solution* from the calibration curve.

Calculate the percentage of oxaliplatin related compound D in the portion of Oxaliplatin taken:

$$\text{Result} = R/10$$

R = concentration ratio of oxaliplatin related compound D, in µg/mL, to the sum of oxaliplatin and oxaliplatin related compound D, in mg/mL, in the *Sample solution* from the calibration curve. ^{15 (USP36)}

Acceptance criteria: NMT 0.1%

SPECIFIC TESTS

• ACIDITY

Sample solution: Dissolve 100 mg in 50 mL of carbon dioxide-free water, and add 0.5 mL of phenolphthalein TS.

Acceptance criteria: The solution is colorless, and NMT 0.6 mL of 0.01 M sodium hydroxide is required to change the color to pink.

• **BACTERIAL ENDOTOXINS TEST** <85>: NMT 1.0 USP Endotoxin Unit/mg of oxaliplatin

• LOSS ON DRYING <731>

Analysis: Dry 1 g at 100°–105° for 2 h.

Acceptance criteria: NMT 0.5%

• **MICROBIAL ENUMERATION TESTS** <61> and **TESTS FOR SPECIFIED MICROORGANISMS** <62>: The total aerobic microbial count does not exceed 20 cfu/g, and the total combined molds and yeast count does not exceed 5 cfu/g.

• OPTICAL ROTATION, *Specific Rotation* <781S>

Sample solution: 5 mg/mL in water

Acceptance criteria: Between +74.5° and +78.0°, measured at 20°

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light. Store at room temperature.

• USP REFERENCE STANDARDS <11>

USP Endotoxin RS

USP Oxaliplatin RS

USP Oxaliplatin Related Compound A RS

Oxalic acid dihydrate.

C₂H₂O₄ · 2H₂O 126.07

USP Oxaliplatin Related Compound B RS

[SP-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N,N'*) dinitratoplatinum(II).

C₆H₁₄N₄O₆Pt 433.28

USP Oxaliplatin Related Compound C RS

[1*R-trans*-(1,2-Cyclohexanediamine-*N,N'*)]-*trans*-dihydroxido-[oxalato(2-)-O,O']platinum(IV).

C₈H₁₆N₂O₆Pt 431.30

USP Oxaliplatin Related Compound D RS
cis-(1*S*,2*S*)-1,2-Cyclohexanediamine-*N,N'*][oxalato(2-)-
 O,O']platinum.
 $C_8H_{14}N_2O_4Pt$ 397.29

Oxaliplatin Injection

DEFINITION

Oxaliplatin Injection is a sterile solution of Oxaliplatin in Water for Injection. It contains NLT 90.0% and NMT 110.0% of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$).

IDENTIFICATION

- A. ULTRAVIOLET ABSORPTION (197U)**
Sample solution: 100 µg/mL
Medium: Water
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

[NOTE—All HPLC autosampler vials should be made of polypropylene.]

PROCEDURE

Acidified water: Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Acidified water* (1:99)

System suitability solution: 0.1 mg/mL of USP Oxaliplatin RS and 0.1 mg/mL of USP Oxaliplatin System Suitability RS in water. [NOTE—USP Oxaliplatin System Suitability RS is [SP-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N,N'*) dichloridoplatinum(II).]

Standard solution: 0.1 mg/mL of USP Oxaliplatin RS in water

Sample solution: 0.1 mg/mL of oxaliplatin in water, from the combined contents of NLT three vials of Injection

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for USP Oxaliplatin System Suitability RS and oxaliplatin are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between USP Oxaliplatin System Suitability RS and oxaliplatin

Tailing factor: NMT 2.0 for the oxaliplatin peak

Relative standard deviation: NMT 1.0% for the oxaliplatin peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of oxaliplatin ($C_8H_{14}N_2O_4Pt$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Oxaliplatin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

LIMIT OF OXALIC ACID

[NOTE—All HPLC autosampler vials should be made of polypropylene.]

Solution A: Dissolve 1.36 g of monobasic potassium phosphate in 10 mL of 10% tetrabutylammonium hydroxide, dilute with water to 1 L, and adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Solution A* (1:4)

Standard solution: 35 µg/mL of USP Oxaliplatin Related Compound A RS in water. [NOTE—USP Oxaliplatin Related Compound A RS is available as dihydrate oxalic acid.]

System suitability solution: 0.1 mg/mL of succinic acid in the *Standard solution*

Sensitivity solution: 3.5 µg/mL of USP Oxaliplatin Related Compound A RS in water from the *Standard solution*

Sample solution: Combined contents of NLT three vials of Injection

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*

[NOTE—The relative retention times for succinic acid and oxalic acid are 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between succinic acid and oxalic acid, *System suitability solution*

Tailing factor: 0.5–2.0 for the oxalic acid peak, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of oxalic acid from the *Sample solution*

r_S = peak response of oxalic acid from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound A RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of anhydrous oxalic acid, 90.03

M_{r2} = molecular weight of oxaliplatin related compound A, 126.07

Acceptance criteria: NMT 0.6%

Change to read:

LIMIT OF (SP-4-2)-DIAQUA[(1*R*,2*R*)-CYCLOHEXANE-1,2-DIAMINE-*N,N'*]PLATINUM AND UNSPECIFIED IMPURITIES

[NOTE—All HPLC autosampler vials should be made of polypropylene.]

Solution A: Dissolve 1.36 g of monobasic potassium phosphate and 0.55 g of sodium heptanesulfonate in

1 L of water. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Methanol and *Solution A* (19:81)

Solution C: Methanol and *Solution A* (50.5: 49.5)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	100	0
45.0	0	100
45.5	100	0
53.0	100	0

System suitability solution: 2 mg/mL of USP Oxaliplatin RS in 0.005 M sodium hydroxide. Allow this solution to stand at room temperature for at least 5 days. Transfer 5 mL of this solution into a 50-mL volumetric flask, and dilute with water to volume. [NOTE—The preparation of the *System suitability solution* forms (SP-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum and diaquodiaminocyclohexaneplatinum dimer.]

Standard stock solution: Transfer a weighed quantity of USP Oxaliplatin Related Compound B RS into a suitable volumetric flask, add a volume of methanol equivalent to about 25% of the final volume, and sonicate for approximately 2 min to disperse the solids. Add a volume of 0.01 M nitric acid equivalent to about 65% of the final volume, and sonicate for approximately 30 min to dissolve. Allow to cool if necessary, and dilute with 0.01 M nitric acid to volume to obtain a solution with a concentration of 0.125 mg/mL.

Standard solution: 31.25 µg/mL of USP Oxaliplatin Related Compound B RS in 0.01 M nitric acid, from the *Standard stock solution*. [NOTE—USP Oxaliplatin Related Compound B RS is converted to (SP-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum in the *Standard solution* preparation.]

Sample solution: Combined contents of NLT three vials of Injection

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 7.5-cm; 3-µm packing L1

Column temperature: 10°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 8.0 between the peaks of (SP-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum and diaquodiaminocyclohexaneplatinum dimer, *System suitability solution*

Tailing factor: NMT 2.0 for the (SP-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum peak, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of (SP-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum from the *Standard solution*

C_S = concentration of USP Oxaliplatin Related Compound B RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of oxaliplatin in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of (SP-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum, 345.30

M_{r2} = molecular weight of oxaliplatin related compound B, 433.28

F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria

Individual impurities: See *Table 2*.

Total impurities: NMT 2.45%, from *Limit of Oxalic Acid* and *Limit of (SP-4-2)-Diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N,N'*]platinum and Unspecified Impurities*

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
(SP-4-2)-Diaqua[(1 <i>R</i> ,2 <i>R</i>)-cyclohexane-1,2-diamine- <i>N,N'</i>]platinum	1.0	1.0	0.65
Diaquodiaminocyclohexaneplatinum dimer ^a	1.4	2.5	0.50
Any individual unspecified impurity	—	4.0	0.2% (RB 1-Oct-2012)

^a (SP-4-2)-Di-µ-oxobis[(1*R*,2*R*)-cyclohexane-1,2-diamine-*kN,kN'*]diplatinum.

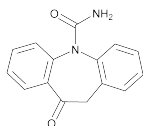
SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST** (85): It contains NMT 1.0 USP Endotoxin Unit/mg of oxaliplatin.
- **STERILITY TESTS** (71): It meets the requirements when tested as directed for *Membrane Filtration* in the *Test for Sterility of the Product to Be Examined*.
- **pH** (791): 4.0–7.0 using a polymer combination electrode
- **PARTICULATE MATTER IN INJECTIONS** (788): It meets the requirements for small-volume injections.
- **OTHER REQUIREMENTS:** It meets the requirements in *Injections* (1).

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in single-dose or multiple-dose containers, preferably of Type I glass, protected from light. Store at controlled room temperature. Do not freeze.
- **LABELING:** Label it to indicate that it is to be diluted with a 5% dextrose solution. Oxaliplatin Injection must not be diluted in sodium chloride solutions or in chloride-containing solutions.
- **USP REFERENCE STANDARDS** (11)
 - USP Endotoxin RS
 - USP Oxaliplatin RS
 - USP Oxaliplatin Related Compound A RS
 - Oxalic acid dihydrate.
C₂H₂O₄ · 2H₂O 126.07
 - USP Oxaliplatin Related Compound B RS
 - [SP-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N,N'*) dinitratoplatinum(II).
C₆H₁₄N₄O₆Pt 433.28
 - USP Oxaliplatin System Suitability RS
 - [SP-4-2-(1*R-trans*)]-(1,2-Cyclohexanediamine-*N,N'*) dichloridoplatinum(II).
C₆H₁₄Cl₂N₂Pt 380.17

Oxcarbazepine



$C_{15}H_{12}N_2O_2$ 252.27
 5*H*-Dibenz[*b,f*]azepine-5-carboxamide, 10,11-dihydro-10-oxo-;
 10,11-Dihydro-10-oxo-5*H*-dibenz[*b,f*]azepine-5-carboxamide [28721-07-5].

DEFINITION

Oxcarbazepine contains NLT 98.0% and NMT 102.0% of oxcarbazepine ($C_{15}H_{12}N_2O_2$), calculated on the anhydrous basis.

IDENTIFICATION

- A. INFRARED ABSORPTION** (197K)
 [NOTE—If the spectrum obtained shows differences, dissolve the substance to be examined in chloroform, and evaporate to dryness. Compare the spectrum of the residue to that of a similarly prepared USP Oxcarbazepine RS.]
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Buffer: 6.8 g/L of monobasic potassium phosphate in water. For each liter prepared, add 2 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 6.0 ± 0.1 .

Mobile phase: Methanol, acetonitrile, and *Buffer* (11:8:31)

Standard solution: 0.1 mg/mL of USP Oxcarbazepine RS in *Mobile phase*

Sample solution: 0.1 mg/mL of Oxcarbazepine in *Mobile phase*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of oxcarbazepine ($C_{15}H_{12}N_2O_2$) in the portion of Oxcarbazepine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Oxcarbazepine RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxcarbazepine in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- RESIDUE ON IGNITION** (281): NMT 0.1%
- HEAVY METALS**, *Method II* (231): NMT 10 ppm

Add the following:

ORGANIC IMPURITIES, PROCEDURE 1

[NOTE—If oxcarbazepine related compound A and oxcarbazepine related compound B are known process impurities, *Organic Impurities, Procedure 2* is recommended.]

Mobile phase: Prepare as directed in the *Assay*.

System suitability solution: 0.1 mg/mL each of USP Oxcarbazepine RS and USP Carbamazepine RS in *Mobile phase*

Standard solution: 0.25 μ g/mL of USP Oxcarbazepine RS in *Mobile phase*

Sample solution: 0.5 mg/mL of Oxcarbazepine in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*, except to use a run time 10 times the retention time of oxcarbazepine.

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 8.0 between oxcarbazepine and carbamazepine, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oxcarbazepine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of oxcarbazepine from the *Standard solution*

C_S = concentration of USP Oxcarbazepine RS in the *Standard solution* (mg/mL)

C_U = concentration of Oxcarbazepine in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxcarbazepine	1.0	1.0	—
Carbamazepine ^a	1.7	1.9	0.5
Dibenzazepinone ^b	2.1	1.2	0.05
Methoxycarbamazepine ^c	2.5	1.6	0.05
Carbamazepine related compound B ^d	7.4	1.3	0.05
Methoxydibenzazepine ^e	7.9	1.5	0.05
Any individual unspecified impurity	—	1.0	0.05
Total impurities	—	—	1.0

^a 5*H*-Dibenz[*b,f*]azepine-5-carboxamide.

^b 10(11*H*)-Oxo-5*H*-dibenz[*b,f*]azepine.

^c 10-Methoxy-5*H*-dibenz[*b,f*]azepine-5-carboxamide.

^d 5*H*-Dibenz[*b,f*]azepine.

^e 10-Methoxy-5*H*-dibenz[*b,f*]azepine.

Add the following:**• ORGANIC IMPURITIES, PROCEDURE 2**

Buffer A: 0.004 mol/L of monobasic potassium phosphate and 0.063 mol/L of dibasic sodium phosphate

Buffer B: To 1 L of 3.6 g/L edetate disodium in water add 1 L of *Buffer A*.

Diluent: 1.8 g/L of ascorbic acid in water

Solution A: Acetonitrile, tetrahydrofuran, *Buffer B*, and water (1:2:2:15)

Solution B: Acetonitrile, tetrahydrofuran, *Buffer B*, and water (6:1:1:2)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
1	80	20
29	30	70
30	30	70
33	80	20
42	80	20

System suitability solution: 2 µg/mL each of USP Oxcarbazepine Related Compound A RS, USP Oxcarbazepine Related Compound B RS, USP Oxcarbazepine Related Compound D RS, and USP Oxcarbazepine Related Compound E RS in a 1:1 mixture of acetonitrile and *Diluent*

Standard stock solution: 0.1 mg/mL of USP Oxcarbazepine RS in acetonitrile

Standard solution: 2 µg/mL of USP Oxcarbazepine RS in a 1:1 mixture of acetonitrile and *Diluent*

Sample solution: 1.0 mg/mL of Oxcarbazepine in a 1:1 mixture of acetonitrile and *Diluent*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Column temperature: 50°

Flow rate: 0.8 mL/min

Injection volume: 50 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.0 between oxcarbazepine related compound A and oxcarbazepine related compound B; NLT 1.2 between oxcarbazepine related compound D and oxcarbazepine related compound E, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oxcarbazepine taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

r_u = peak response of each impurity from the *Sample solution*

r_s = peak response of oxcarbazepine from the *Standard solution*

C_s = concentration of USP Oxcarbazepine RS in the *Standard solution* (mg/mL)

C_u = concentration of Oxcarbazepine in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. [NOTE—Disregard any peak below 0.03%.]

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxcarbazepine related compound F ^a	0.76	0.59	0.2
Oxcarbazepine	1.0	—	—
N-Carbamoyl oxcarbazepine ^b	1.1	0.91	0.05
Oxcarbazepine related compound A ^c	1.2	1.1	0.2
Oxcarbazepine related compound B ^d	1.3	1.1	0.1
Dibenzazepinodione ^e	1.7	2.0	0.1
Oxcarbazepine related compound D ^f	2.3	1.7	0.2
Oxcarbazepine related compound E ^g	2.4	3.3	0.05
Any individual unspecified impurity	—	1.0	0.05
Total impurities	—	—	1.0

^a 10,11-Dioxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.

^b N-Carbamoyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.

^c N-Formyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.

^d N-Acetyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.

^e 5H-Dibenzo[b,f]azepine-10,11-dione.

^f 10-(10-Oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamido)-5H-dibenzo[b,f]azepine-5-carboxamide.

^g 10(11H)-Oxo-5H-dibenzo[b,f]azepine.

■1S (USP36)

SPECIFIC TESTS

• **WATER DETERMINATION, Method Ia** <921>: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

• **LABELING:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.■1S (USP36)

Change to read:**• USP REFERENCE STANDARDS <11>**

USP Oxcarbazepine RS

■USP Carbamazepine RS

USP Oxcarbazepine Related Compound A RS

N-Formyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.

C₁₆H₁₂N₂O₃ 280.28

USP Oxcarbazepine Related Compound B RS

N-Acetyl-10-oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide.

C₁₇H₁₄N₂O₃ 294.30

USP Oxcarbazepine Related Compound D RS

10-(10-Oxo-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamido)-5H-dibenzo[b,f]azepine-5-carboxamide.

C₃₀H₂₂N₄O₃ 486.52

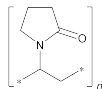
USP Oxcarbazepine Related Compound E RS

10(11H)-Oxo-5H-Dibenzo[b,f]azepine.

C₁₄H₁₁NO 209.24■1S (USP36)

Povidone

Portions of the monograph text that are national *USP* text, and are not part of the harmonized text, are marked with symbols (♦) to specify this fact.



$(C_6H_9NO)_n$

2-Pyrrolidinone, 1-ethenyl-, homopolymer;

1-Vinyl-2-pyrrolidinone polymer [9003-39-8].

DEFINITION

Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. The different types of Povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value (see *Specific Tests, K-value*). The K-value of Povidone having a stated (nominal) K-value of 15 or less is NLT 85.0% and NMT 115.0% of the stated values. The K-value of Povidone having a stated K-value or a stated K-value range with an average of more than 15 is NLT 90.0% and NMT 108.0% of the stated value or of the average of the stated range. It contains NLT 11.5% and NMT 12.8% of nitrogen (N: 14.01), calculated on the anhydrous basis. It has a nominal K-value of NLT 10 and NMT 120. The nominal K-value is shown on the label.

IDENTIFICATION

Add the following:

♦ A. INFRARED ABSORPTION (197K)

Sample: Dry at 105° for 6 h. 15 (USP36)

Change to read:

♦ B. 15 (USP36)

Sample solution: 20 mg/mL of Povidone

Analysis: To 10 mL of the *Sample solution* add 20 mL of 1 N hydrochloric acid and 5 mL of potassium dichromate TS.

Acceptance criteria: An orange-yellow precipitate is formed.♦

Change to read:

♦ C. 15 (USP36)

Solution A: Dissolve 75 mg of cobalt nitrate and 300 mg of ammonium thiocyanate in 2 mL of water.

Sample solution: 20 mg/mL of Povidone

Analysis: Combine *Solution A* and 5 mL of the *Sample solution*, and render the resulting solution acidic by the addition of 3 N hydrochloric acid.

Acceptance criteria: A pale blue precipitate is formed.♦

Change to read:

♦ D. 15 (USP36)

Sample solution: 5 mg/mL of Povidone

Analysis: To 5 mL of the *Sample solution* add a few drops of iodine TS.

Acceptance criteria: A deep red color is produced.♦

Change to read:

♦ E. 15 (USP36)

Sample solution: 50 mg/mL of Povidone in water

Acceptance criteria: The substance dissolves.

ASSAY

♦ NITROGEN DETERMINATION, Method II (461)

Sample: 0.1 g of Povidone

Analysis: Proceed as directed, using the *Sample*. In the *Procedure*, omit the use of hydrogen peroxide, and use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33:1:1) instead of potassium sulfate and cupric sulfate (10:1). Heat until a clear, light-green solution is obtained. Heat for an additional 45 min, and proceed as directed for the *Procedure*, beginning with "Cautiously add to the digestion mixture 70 mL of water".

Acceptance criteria: 11.5%–12.8% on the anhydrous basis

IMPURITIES

♦ RESIDUE ON IGNITION (281): NMT 0.1%

♦ LEAD (251)

Test preparation: 1.0 g in 25 mL of water

Acceptance criteria: NMT 10 ppm

Change to read:

♦ LIMIT OF ALDEHYDES

Solution A: Transfer 8.3 g of potassium pyrophosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N hydrochloric acid to a pH of 9.0, and dilute with water to volume.

Solution B: Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, and dissolve in 10.0 mL of water. [NOTE—This solution is stable for 8 h at 4°.]

Solution C: Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, and dissolve in 10.0 mL of *Solution A*. [NOTE—This solution is stable for four weeks at 4°.]

Standard solution: Add 2 mL of water to a glass weighing bottle, and weigh. Add 100 mg (0.13 mL) of freshly distilled acetaldehyde, and weigh. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water, transferring each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water to volume. Store at 4° for about 20 h. Pipet 1 mL of this solution into a 100-mL volumetric flask, and dilute with water to volume.

Sample solution: 20 mg/mL of Povidone in *Solution A*. Insert a stopper into the flask, heat at 60° for 1 h, and cool to room temperature.

Blank: Water

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV

Analytical wavelength: 340 nm

Cell: 1 cm

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank* Pipet 0.5 mL each of the *Standard solution*, *Sample solution*, and *Blank* into separate cells. Add 2.5 mL of *Solution A* and 0.2 mL of *Solution C* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2–3 min at 22 ± 2°. Determine the absorbances of the solutions using the *Blank* as the reference. Add 0.05 mL of *Solution B* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 min at 22 ± 2°. Determine the ab-

sorbances of the solutions, using the *Blank* as the reference.

Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Povidone taken:

$$\bullet \text{Result} = 100 \times (C_S/C_U) \times \{[(A_{U2} - A_{U1}) - (A_{B2} - A_{B1})] / [(A_{S2} - A_{S1}) - (A_{B2} - A_{B1})]\}$$

C_S = concentration of acetaldehyde in the *Standard solution* (mg/mL)

C_U = concentration of *Sample solution* (mg/mL) • (ERR 1-Oct-2012)

A_{U2} = absorbance of the solution from the *Sample solution*, after addition of *Solution B*

A_{U1} = absorbance of the solution from the *Sample solution*, before addition of *Solution B*

A_{B2} = absorbance of the solution from the *Blank*, after addition of *Solution B*

A_{B1} = absorbance of the solution from the *Blank*, before addition of *Solution B*

A_{S2} = absorbance of the solution from the *Standard solution*, after addition of *Solution B*

A_{S1} = absorbance of the solution from the *Standard solution*, before addition of *Solution B*

Acceptance criteria: NMT 0.05%

• LIMIT OF HYDRAZINE

Standard solution: 9.38 µg/mL of salicylaldazine in toluene

Sample solution: Transfer 2.5 g to a 50-mL centrifuge tube, add 25 mL of water, and mix to dissolve. Add 500 µL of a solution (1 in 20) of salicylaldehyde in methanol. Swirl, and heat in a water bath at 60° for 15 min. Allow to cool, and add 2.0 mL of toluene. Insert a stopper in the tube, shake vigorously for 2 min, and centrifuge. Use the clear upper toluene layer in the centrifuge tube as the *Sample solution*.

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of dimethylsilanized chromatographic silica gel mixture

Application volume: 10 µL

Developing solvent system: Methanol and water (2:1)

Analytical wavelength: UV 365 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Proceed as directed in the chapter. Allow the spots to dry, and develop the chromatogram with the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Locate the spots on the plate by examination under UV light. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate.

Acceptance criteria: Salicylaldazine appears as a fluorescent spot having an R_f value of 0.3; and the fluorescence of any salicylaldazine spot from the *Sample solution* is not more intense than that produced by the spot from the *Standard solution* (NMT 1 ppm of hydrazine).

Change to read:

• VINYLPIRROLIDINONE

Mobile phase: Methanol and water (1:4)

System suitability solution: Transfer 10 mg of vinylpyrrolidinone and 500 mg of vinyl acetate to a 100-mL volumetric flask, and dissolve in and dilute with methanol to volume. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Standard stock solution: 5 µg/mL of vinylpyrrolidinone in methanol

Standard solution: 0.25 µg/mL from vinylpyrrolidinone *Standard stock solution* in *Mobile phase*

Sample solution: 25 mg/mL of Povidone in *Mobile phase*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 235 nm

Columns

Guard: 4.0-mm × 2.5-cm; packing L1

Analytical: 4.0-mm × 25-cm; 5-µm packing L1

[NOTE—The analysis can also be performed with a 4.0-mm × 30-mm or a 4.6-mm × 30-mm guard column • (ERR 1-Oct-2012) containing packing L1 • (ERR 1-May-2012) and with a 4.6- × 25-cm analytical column containing 5-µm packing L1 • (ERR 1-May-2012).]

Column temperature: 40°

[NOTE—Adjust the flow rate so that the retention time of vinylpyrrolidinone is about 10 min.]

Injection volume: 50 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between vinylpyrrolidinone and vinyl acetate, *System suitability solution*

Relative standard deviation: NMT 2.0% of vinylpyrrolidinone for 6 injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms, and measure the responses for the vinylpyrrolidinone peak. [NOTE—If necessary, after each injection of the *Sample solution* wash the polymeric material of Povidone from the guard column by passing the *Mobile phase* through the column backwards for 30 min at the same flow rate.]

Calculate the percentage of vinylpyrrolidinone in the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of vinylpyrrolidinone from the *Sample solution*

r_S = peak response of vinylpyrrolidinone from the *Standard solution*

C_S = concentration of vinylpyrrolidinone in the *Standard solution* (mg/mL)

C_U = concentration of Povidone in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.001%

• 2-PYRROLIDINONE

Mobile phase: Water adjusted with phosphoric acid to a pH of 2.4

Standard solution: 30 µg/mL of 2-pyrrolidinone in water

Sample solution: 5 mg/mL of Povidone in water

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 205 nm

Columns

Guard: 4.0-mm × 2.5-cm; packing L1

Analytical: 4.0-mm × 25-cm; 5-µm packing L1

Column temperature: 30°

[NOTE—Adjust the flow rate so that the retention time of 2-pyrrolidinone is about 11 min.]

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% of 2-pyrrolidinone for 6 injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms, and measure the responses for the 2-pyrrolidinone peak. [NOTE—After each injection of the *Sample solution* wash the polymeric mate-

rial of Povidone from the guard column by passing the *Mobile phase* through the column backwards for 30 min at the same flow rate.]

Calculate the percentage of 2-pyrrolidinone in the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- r_U = peak response of 2-pyrrolidinone from the *Sample solution*
 r_S = peak response of 2-pyrrolidinone from the *Standard solution*
 C_S = concentration of 2-pyrrolidinone in the *Standard solution* (mg/mL)
 C_U = concentration of Povidone in the *Sample solution* (mg/mL), calculated on the anhydrous basis

Acceptance criteria: NMT 3.0%

• PEROXIDES

Sample solution: 40 mg/mL of Povidone in water, calculated on the anhydrous basis

Blank: To 25 mL of the *Sample solution* add 2 mL of 13% sulfuric acid.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV-Vis

Analytical wavelength: 405 nm

Cell: 1 cm

Analysis

Sample: *Sample solution*

To 25 mL of the *Sample solution* add 2 mL of titanium trichloride-sulfuric acid TS, and allow to stand for 30 min. Measure the absorbance of a portion of this solution against the *Blank*.

Acceptance criteria: NMT 0.35, corresponding to NMT 400 ppm, expressed as H₂O₂

• FORMIC ACID

Mobile phase: Diluted perchloric acid (5 in 1000)

Standard solution: 10 µg/mL of formic acid in water

Sample stock solution: 20 mg/mL of Povidone in water

Sample solution: Transfer a suspension of strongly acidic ion-exchange resin (use the hydrogen form of ion-exchange resin) in water to a column of about 0.8 cm in inside diameter to give a packing depth of about 20 mm in length, and keep the strongly acidic ion-exchange resin layer constantly immersed in water. Pour 5 mL of water, and adjust the flow rate so that water drops at a rate of about 20 drops/min. When the level of the water is near the top of the strongly acidic ion-exchange resin layer, add 100 mL of the *Sample stock solution* into the column. After dropping 2 mL of the solution, collect 1.5 mL of the solution, and use this as the *Sample solution*.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4- to 8-mm × 25- to 30-cm; 5- to 10-µm packing L17

Column temperature: 30°

[NOTE—Adjust the flow rate so that the retention time of formic acid is about 11 min.]

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0% of formic acid for 6 injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Record the chromatograms, and measure the responses for the formic acid peak.

Calculate the percentage of formic acid in the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- r_U = peak response of formic acid from the *Sample solution*
 r_S = peak response of formic acid from the *Standard solution*
 C_S = concentration of formic acid in the *Standard solution* (mg/mL)
 C_U = concentration of Povidone in the *Sample solution* (mg/mL), calculated on the anhydrous basis

Acceptance criteria: NMT 0.5%

SPECIFIC TESTS

• PH (791)

Sample solution: 50 mg/mL in water

Acceptance criteria: 3.0–5.0 for Povidone having a nominal K-value of 30 or less; 4.0–7.0 for Povidone having a nominal K-value greater than 30

• WATER DETERMINATION, Method I (921): NMT 5.0%

• K-VALUE

Sample solution: Weigh a quantity of undried Povidone equivalent, on the anhydrous basis, to the amount specified in *Table 1*.

Table 1

Nominal K-value	Quantity (g)
≤18	5.00
>18 to ≤95	1.00
>95	0.10

Dissolve it in 50 mL of water in a 100-mL volumetric flask, and dilute to volume. Allow to stand for 1 h.

Analysis

Sample: *Sample solution*

Determine the viscosity of the *Sample solution*, using a capillary-tube viscometer (see *Viscosity* (911)), at 25 ± 0.2°. Calculate the K-value of Povidone:

$$\text{Result} = \left[\sqrt{300c \log z + (c + 1.5c \log z)^2} + 1.5c \log z - c \right] / (0.15c + 0.003c^2)$$

c = weight, on the anhydrous basis, of the specimen tested in each 100.0 mL of solution (g)

z = viscosity of the *Sample solution* relative to that of water

Acceptance criteria

K-value of Povidone having a stated (nominal) K-value of NMT 15: 85.0%–115.0% of the stated values

K-value of Povidone having a stated K-value or a stated K-value range with an average of more than 15: 90.0%–108.0% of the stated value or of the average of the stated range

ADDITIONAL REQUIREMENTS

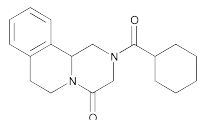
- **PACKAGING AND STORAGE:** Preserve in tight containers.♦
- **LABELING:** Label it to state, as part of the official title, the K-value or K-value range of Povidone.♦

Add the following:

• USP REFERENCE STANDARDS (11)

USP Povidone RS, **1S** (USP36)

Praziquantel



$C_{19}H_{24}N_2O_2$ 312.41
 4H-Pyrazino[2,1-a]isoquinolin-4-one, 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-;
 2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one [55268-74-1].

DEFINITION

Praziquantel contains NLT 98.5% and NMT 101.0% of praziquantel ($C_{19}H_{24}N_2O_2$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)

Add the following:

- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■ US (USP36)

ASSAY

• PROCEDURE

Mobile phase: Acetonitrile and water (60:40)
Standard solution: 0.18 mg/mL of USP Praziquantel RS in *Mobile phase*

Sample solution: 0.18 mg/mL of Praziquantel in *Mobile phase*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4-mm × 25-cm; 10-μm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of praziquantel ($C_{19}H_{24}N_2O_2$) in the portion of Praziquantel taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Praziquantel RS in the *Standard solution* (mg/mL)

C_U = concentration of Praziquantel in the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–101.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%

• LIMIT OF PHOSPHATE

Solution A: Dissolve 250 mg of cupric sulfate and 4.5 g of ammonium acetate in sufficient 2 N acetic acid to obtain 100 mL of solution.

Solution B: 30 mg/mL of ammonium molybdate

Solution C: Grind in a mortar 5 g of sodium sulfite, 94.3 g of sodium metabisulfite, and 700 mg of 4-amino-3-hydroxy-1-naphthalenesulfonic acid. Dissolve

1.5 g of this mixture in 10 mL of water, heating gently if necessary. Use this solution only when freshly prepared.

Standard stock solution: 100 μg/mL of phosphate (PO_4^{3-}) prepared as follows. Dissolve 143.3 mg of dried monobasic potassium phosphate in water to make 1000 mL of solution.

Standard solution: 5 μg/mL of phosphate (PO_4^{3-}) from the *Standard stock solution*

Sample solution: 10 mg/mL of Praziquantel, prepared as follows. Add 30 mL of water to 500 mg of sample, and heat to boiling. Allow to cool, and filter, collecting the filtrate in a 50-mL volumetric flask. Wash the filter with water, collect the washings in the volumetric flask, and dilute with water to volume.

Analysis: Treat 10 mL of the *Standard solution* and 10 mL of the *Sample solution* as follows. To each, add 5 mL of *Solution A*, 2 mL of *Solution B*, 1 mL of *Solution C*, and 1 mL of perchloric acid solution (3 in 100); mix; and allow to stand for 15 min.

Acceptance criteria: The *Sample solution* does not have a blue color that is darker than that of the *Standard solution* (0.05%).

- **HEAVY METALS, Method II** (231): NMT 20 μg/g

• ORGANIC IMPURITIES

Mobile phase and Chromatographic system: Proceed as directed in the *Assay*.

Standard solution: 0.04 mg/mL each of USP Praziquantel Related Compound A RS, USP Praziquantel Related Compound B RS, and USP Praziquantel Related Compound C RS in *Mobile phase*

Sample solution: 20 mg/mL of Praziquantel in *Mobile phase*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentages of praziquantel related compound A, praziquantel related compound B, or praziquantel related compound C in the portion of Praziquantel taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of praziquantel related compound A, praziquantel related compound B, or praziquantel related compound C from the *Sample solution*

r_S = peak response of praziquantel related compound A, praziquantel related compound B, or praziquantel related compound C from the *Standard solution*

C_S = concentration of USP Praziquantel Related Compound A RS, USP Praziquantel Related Compound B RS, or USP Praziquantel Related Compound C RS in the *Standard solution* (mg/mL)

C_U = concentration of Praziquantel in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Praziquantel related compound A ^a	0.8	0.2
Praziquantel	1.0	—

^a 2-Benzoyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.

^b 2-(Cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.

^c 2-(N-Formylhexahydrohippuroyl)-1,2,3,4-tetrahydroisoquinolin-1-one.

Table 1 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Praziquantel related compound B ^b	1.8	0.2
Praziquantel related compound C ^c	2.1	0.2

^a 2-Benzoyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.^b 2-(Cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.^c 2-(N-Formylhexahydrohippuroyl-1,2,3,4-tetrahydroisoquinolin-1-one.**SPECIFIC TESTS****Delete the following:****MELTING RANGE OR TEMPERATURE (741):**136°–142° ■^{1S} (USP36)**LOSS ON DRYING (731)**

Analysis: Dry a sample in a vacuum at a pressure not exceeding 5 mm of mercury at 50° over phosphorus pentoxide for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.

USP REFERENCE STANDARDS (11)

USP Praziquantel RS

USP Praziquantel Related Compound A RS

2-Benzoyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.

C₁₉H₁₈N₂O₂ 306.37

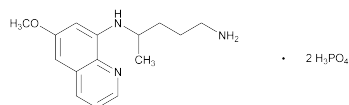
USP Praziquantel Related Compound B RS

2-(Cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4H-pyrazino [2,1-a]isoquinolin-4-one.

C₁₉H₂₂N₂O₂ 310.40

USP Praziquantel Related Compound C RS

2-(N-Formylhexahydrohippuroyl-1,2,3,4-tetrahydroisoquinolin-1-one.

C₁₉H₂₂N₂O₄ 342.39**Primaquine Phosphate**C₁₅H₂₁N₃O · 2H₃PO₄ 455.341,4-Pentanediamine, N⁴-(6-methoxy-8-quinoliny)-, (±)-, phosphate (1:2);

(±)-8-[(4-Amino-1-methylbutyl)amino]-6-methoxyquinoline phosphate (1:2) [63-45-6].

DEFINITION

Primaquine Phosphate contains NLT 97.0% and NMT 102.0% of primaquine phosphate (C₁₅H₂₁N₃O · 2H₃PO₄), calculated on the dried basis.

IDENTIFICATION

- A. INFRARED ABSORPTION (197K):** Meets the requirements
- B.** The residue obtained by ignition meets the requirements of the test for pyrophosphate, as described in *Identification Tests—General* (191), *Phosphate*.
- C.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**PROCEDURE**

Mobile phase: Acetonitrile, tetrahydrofuran, trifluoroacetic acid, and water (9: 1: 0.1: 90)

Standard solution: 0.4 mg/mL of USP Primaquine Phosphate RS in *Mobile phase*. [NOTE—Sonicate with intermittent shaking to dissolve, if necessary.]

System suitability stock solution: 0.4 mg/mL of USP Primaquine Related Compound A RS in *Mobile phase*

System suitability solution: Transfer 1.0 mL of the *System suitability stock solution* to a 10-mL volumetric flask, and dilute with *Standard solution* to volume.

Sensitivity solution: 0.2 µg/mL of USP Primaquine Phosphate RS from the *Standard solution*

Sample solution: 0.4 mg/mL in *Mobile phase*. [NOTE—Sonicate with intermittent shaking to dissolve, if necessary.]

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 265 nm

Column: 4.6-mm × 75-mm; 3-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: 3 times the retention time of primaquine

System suitability

Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.5 between primaquine and primaquine related compound A, *System suitability solution*

Relative standard deviation: NMT 1.0% for primaquine, *Standard solution*

Signal-to-noise ratio: NLT 10 for the primaquine peak, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of primaquine phosphate (C₁₅H₂₁N₃O · 2H₃PO₄) in the portion of Primaquine Phosphate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Primaquine Phosphate RS in the *Standard solution* (mg/mL)

C_U = concentration of Primaquine Phosphate in the *Sample solution* (mg/mL)

Acceptance criteria: 97.0%–102.0% on the dried basis

IMPURITIES**Change to read:****ORGANIC IMPURITIES**

Mobile phase, Standard solution, System suitability solution, Sensitivity solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the *Assay*.

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Primaquine Phosphate taken:

$$\text{Result} = (r_U/r_S) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of primaquine phosphate from the *Sample solution*

Acceptance criteria: See *Table 1*. Disregard any impurity peak less than 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Specified unidentified impurity	0.24	0.20
Specified unidentified impurity	0.29	0.60
Primaquine related compound A ^a	0.80	2.0
Primaquine	1.0	—
● Secaquine ^b ● (RB 1-Oct-2012)	1.8	● 0.80 ● (RB 1-Oct-2012)
Any other individual impurities	—	0.20
Total impurities	—	3.0

^a 8-[(4-Aminopentyl)amino]-6-methoxyquinoline.^b N³-(6-Methoxyquinolin-8-yl)pentane-1,3-diamine. ● (RB 1-Oct-2012)**SPECIFIC TESTS****• LOSS ON DRYING (731)**

Analysis: Dry a sample at 105° for 2 h.

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS**• PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.**• USP REFERENCE STANDARDS (11)**

USP Primaquine Phosphate RS

USP Primaquine Related Compound A RS

8-[(4-Aminopentyl)amino]-6-methoxyquinoline.

C₁₅H₂₁N₃O 259.35**Add the following:****• Quinapril and Hydrochlorothiazide Tablets****DEFINITION**

Quinapril and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amounts of quinapril (C₂₅H₃₀N₂O₅) and hydrochlorothiazide (C₇H₈ClN₃O₄S₂).

IDENTIFICATION

• A. The relative retention times of the major peaks from the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY**• PROCEDURE**

Buffer: Dissolve 1.36 g/L of monobasic potassium phosphate in water, add 2 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0. Pass through a suitable nylon filter of 0.45-μm pore size.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Buffer (%)	Acetonitrile (%)
0	75	25
8	40	60
12	40	60
13	75	25
18	75	25

Diluent: Acetonitrile and *Buffer* (50:50)

Quinapril hydrochloride standard stock solution: 0.45 mg/mL of USP Quinapril Hydrochloride RS in *Diluent*

Hydrochlorothiazide standard stock solution: 0.5 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

Standard solution: Dilute *Quinapril hydrochloride standard stock solution* and *Hydrochlorothiazide standard stock solution* with *Diluent* to final volume as given in *Table 2*.

Table 2

Tablet Strength Quinapril Hydrochloride/Hydrochlorothiazide (mg/mg)	Quinapril Hydrochloride Standard Stock Solution (mL)	Hydrochlorothiazide Standard Stock Solution (mL)	Final Volume (mL)
10/12.5	5	5	100
20/12.5	10	5	200
20/25	5	5	100

Sample stock solution: Transfer 5 Tablets into a 250-mL volumetric flask, add 50 mL of *Diluent*, and sonicate for 15 min. Add about 50 mL of acetonitrile, and sonicate for 15 min with shaking. Add 50 mL of *Diluent*, and sonicate for 15 min. Dilute with *Diluent* to volume.

Sample solution: 0.02 mg/mL of quinapril in *Diluent* from the *Sample stock solution*. [NOTE—The hydrochlorothiazide concentration may vary depending on the ratio of quinapril hydrochloride to hydrochlorothiazide in the Tablet.]

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-μm packing L1

Column oven temperature: 35°

Flow rate: 1 mL/min

Injection volume: 20 μL

System suitability

Samples: *Standard solution*

Suitability requirements

Column efficiency: NLT 2500 theoretical plates from both quinapril and hydrochlorothiazide peaks

Tailing factor: NMT 2.0 for both quinapril and hydrochlorothiazide peaks

Relative standard deviation: NMT 2.0% for both quinapril and hydrochlorothiazide peaks

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of quinapril (C₂₅H₃₀N₂O₅) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of quinapril from the *Sample solution*

r_S = peak response of quinapril from the *Standard solution*

C_S = concentration of USP Quinapril Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of quinapril in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of quinapril, 438.52

M_{r2} = molecular weight of quinapril hydrochloride, 474.98

Calculate the percentage of hydrochlorothiazide (C₇H₈ClN₃O₄S₂) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- r_U = peak response of hydrochlorothiazide from the *Sample solution*
 r_S = peak response of hydrochlorothiazide from the *Standard solution*
 C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

• DISSOLUTION (711)

Buffer, Mobile phase, Chromatographic system, and System suitability: Proceed as directed in the Assay.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 20 min

Quinapril hydrochloride standard stock solution:

0.45 mg/mL of USP Quinapril Hydrochloride RS in *Diluent*

Hydrochlorothiazide standard stock solution:

0.55 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

Standard solution: Prepare dilutions of Quinapril hydrochloride standard stock solution and Hydrochlorothiazide standard stock solution in *Medium* as directed in Table 3.

Table 3

Tablet Strength Quinapril Hydrochloride/ Hydrochlorothiazide (mg/mg)	Quinapril Hydrochloride Standard Stock Solution (mL)	Hydrochlorothiazide Standard Stock Solution (mL)	Final Volume (mL)
10/12.5	5	5	200
20/12.5	10	5	200
20/25	5	5	100

Sample solution: Pass a portion of the solution under test through a suitable nylon filter of 0.45- μ m pore size, discarding the first few mL.

Analysis

Calculate the percentage of quinapril ($C_{25}H_{30}N_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

- r_U = peak response of quinapril from the *Sample solution*
 r_S = peak response of quinapril from the *Standard solution*
 C_S = concentration of USP Quinapril Hydrochloride RS in the *Standard solution*
 L = label claim for quinapril hydrochloride (mg/Tablet)
 V = volume of *Medium*, 900 mL
 M_{r1} = molecular weight of quinapril, 438.52
 M_{r2} = molecular weight of quinapril hydrochloride, 474.98

Calculate the percentage of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

- r_U = peak response of hydrochlorothiazide from the *Sample solution*
 r_S = peak response of hydrochlorothiazide from the *Standard solution*
 C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution*
 L = label claim for hydrochlorothiazide (mg/Tablet)
 V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amounts of each quinapril ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

• ORGANIC IMPURITIES

Buffer and Diluent: Proceed as directed in the Assay.

Mobile phase: See Table 4.

Table 4

Time (min)	Buffer (%)	Acetonitrile (%)
0	90	10
10	60	40
30	30	70
31	90	10
40	90	10

Standard stock solution: 0.45 mg/mL of each USP Quinapril Hydrochloride RS, USP Quinapril Related Compound A RS, and USP Quinapril Related Compound B RS, and 0.50 mg/mL of each USP Hydrochlorothiazide RS and USP Benzothiadiazine Related Compound A RS in *Diluent*

Standard solution: 0.45 μ g/mL of quinapril hydrochloride, quinapril related compound A, and quinapril related compound B, and 0.5 μ g/mL of hydrochlorothiazide and benzothiadiazine related compound A from *Standard stock solution* in *Diluent*

Sample stock solution: Transfer 5 Tablets into a 250-mL volumetric flask, add 50 mL of diluent, and sonicate for 10 min to disperse the Tablets. Add about 50 mL of acetonitrile, and sonicate for 15 min with shaking. Add 50 mL of *Diluent*, and sonicate for 15 min. Dilute with *Diluent* to volume. Pass through a suitable nylon filter of 0.45- μ m pore size.

Sample solution: For Tablet strengths of 10 mg/12.5 mg and 20 mg/12.5 mg of quinapril hydrochloride/hydrochlorothiazide, use *Sample stock solution* as is. For Tablet strength of 20 mg/25 mg of quinapril hydrochloride/hydrochlorothiazide, dilute 5 mL of *Sample stock solution* with *Diluent* to 10 mL.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column oven temperature: 35°

Sample temperature: 5°

Flow rate: 1 mL/min

Injection volume: 20 μ L

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 5000 theoretical plates from both quinapril and hydrochlorothiazide peaks

Tailing factor: NMT 2.0 for both quinapril and hydrochlorothiazide peaks

Relative standard deviation: NMT 5.0% for both quinapril and hydrochlorothiazide peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of quinapril related compound A and quinapril related compound B in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- r_U = peak response of quinapril related compound A or quinapril related compound B from the *Sample solution*

- r_s = peak response of USP Quinapril Related Compound A RS or USP Quinapril Related Compound B RS from the *Standard solution*
- C_s = concentration of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of quinapril in the *Sample solution* (mg/mL)

Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_s) \times (C_s/C_U) \times 100$$

- r_U = peak response of benzothiadiazine related compound A from the *Sample solution*
- r_s = peak response of benzothiadiazine related compound A from the *Standard solution*
- C_s = concentration of USP Benzothiadiazine Related Compound A RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_s) \times (C_s/C_U) \times (M_{r1}/M_{r2}) \times 100$$

- r_U = peak response of each other impurity from the *Sample solution*
- r_s = peak response of quinapril from the *Standard solution*
- C_s = concentration of USP Quinapril Hydrochloride RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of quinapril in the *Sample solution* (mg/mL)
- M_{r1} = molecular weight of quinapril, 438.52
- M_{r2} = molecular weight of quinapril hydrochloride, 474.98

Acceptance criteria: See Table 5.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A ^a	0.42	1.0
Chlorothiazide ^b	0.45	—
Hydrochlorothiazide ^b	0.49	—
5-Chlorohydrochlorothiazide ^b	0.65	—
Quinapril related compound B ^c	0.74	3.0
Hydrochlorothiazide dimer ^b	0.78	—
Quinapril methyl ester ^b	0.91	—
Quinapril ^b	1.00	—
Quinapril isopropyl ester ^b	1.10	—
Hexahydroquinapril ^b	1.23	—
Quinapril related compound A ^d	1.59	1.0
Quinapril, benzyl ester ^b	1.94	—

^a 4-Amino-6-chloro-1,3-benzenedisulfonamide.

^b Process related impurity, monitored in the drug substance.

^c 3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3S-[2(R*)],3R*]]].

^d Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate.

^e Total impurities does not include quinapril related compound B and benzothiadiazine related compound A.

Table 5 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any other individual unspecified impurity	—	0.2
Total impurities ^e	—	2.0

^a 4-Amino-6-chloro-1,3-benzenedisulfonamide.

^b Process related impurity, monitored in the drug substance.

^c 3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3S-[2(R*)],3R*]]].

^d Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate.

^e Total impurities does not include quinapril related compound B and benzothiadiazine related compound A.

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE:** Preserve in well-closed containers, and protect from light. Store at controlled room temperature.

USP REFERENCE STANDARDS (11)

USP Benzothiadiazine Related Compound A RS

4-Amino-6-chloro-1,3-benzenedisulfonamide.

C₆H₈ClN₃O₄S₂ 285.73

USP Hydrochlorothiazide RS

USP Quinapril Hydrochloride RS

USP Quinapril Related Compound A RS

Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate.

C₂₅H₂₈N₂O₄ 420.50

USP Quinapril Related Compound B RS

3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-

3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, 3S-[2(R*),3R*]]-.

C₂₃H₂₆N₂O₅ 410.46 ■1S (USP36)

Quinine Sulfate Capsules

DEFINITION

Quinine Sulfate Capsules contain amounts of quinine sulfate and dihydroquinine sulfate totaling NLT 90.0% and NMT 110.0% of the labeled amount of quinine sulfate, calculated as (C₂₀H₂₄N₂O₂)₂ · H₂SO₄ · 2H₂O.

IDENTIFICATION

A.

Sample: Nominally 100 mg of quinine sulfate from the contents of Capsules

Analysis: Shake the *Sample* with 100 mL of dilute sulfuric acid (1 in 350), and filter.

Acceptance criteria: An appropriate dilution of the filtrate exhibits a vivid blue fluorescence. On the addition of a few drops of hydrochloric acid, the fluorescence disappears.

- B.** The *R_f* value of the principal spot from the *Sample solution* corresponds to that from the *Standard solution A*, as obtained in the test for *Organic Impurities*.

C. IDENTIFICATION TESTS—GENERAL, Sulfate (191)

Sample: Nominally 20 mg of quinine sulfate from the contents of Capsules

Analysis: Shake the *Sample* with 10 mL of dilute hydrochloric acid (1 in 100), and filter.

Acceptance criteria: The filtrate meets the requirements.

- D.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**Change to read:****PROCEDURE**

Solution A: Add 35.0 mL of methanesulfonic acid to 20.0 mL of glacial acetic acid, and dilute with water to 500 mL.

Solution B: Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.

Mobile phase: Acetonitrile, *Solution A*, *Solution B*, and water (100:20:20:860). Adjust with *Solution B* to a pH of 2.6 if the pH is found to be lower.

System suitability solution: 0.2 mg/mL each of USP Quinine Sulfate RS and dihydroquinine, dissolved in 10% of the final volume of methanol. Dilute with *Mobile phase* to volume.

Standard solution: 0.2 mg/mL of USP Quinine Sulfate RS in *Mobile phase*

Sample stock solution: Nominally 1.6 mg/mL of quinine sulfate in methanol prepared as follows. Transfer an amount, equivalent to 160 mg of quinine sulfate from the contents of NLT 20 Capsules, to a 100-mL volumetric flask, add 80 mL of methanol, and shake the flask by mechanical means for 30 min. Dilute with methanol to volume, and filter, discarding the first 10 mL of the filtrate.

Sample solution: Nominally 0.2 mg/mL of quinine sulfate in *Mobile phase* from the *Sample stock solution*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 1 mL/min (USP36)

Injection volume: 50 µL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for quinine and dihydroquinine are 1 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 1.2 between quinine and dihydroquinine

Relative standard deviation: NMT 2.0% for the quinine peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ calculated as the sum of quinine sulfate and dihydroquinine sulfate in the portion of Capsules taken:

$$\text{Result} = [(r_{b,U} + r_{d,U}) / (r_{b,S} + r_{d,S})] \times (C_S / C_U) \times 100$$

$r_{b,U}$ = peak area response of quinine from the *Sample solution*

$r_{d,U}$ = peak area response of dihydroquinine from the *Sample solution*

$r_{b,S}$ = peak area response of quinine from the *Standard solution*

$r_{d,S}$ = peak area response of dihydroquinine from the *Standard solution*

C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of quinine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS**DISSOLUTION <711>**

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Detection: UV maximum at about 248 nm

Standard solution: Prepare a solution of known concentration of USP Quinine Sulfate RS in *Medium*.

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ dissolved.

Tolerances: NLT 75% (Q) of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ is dissolved.

UNIFORMITY OF DOSAGE UNITS <905>**Procedure for content uniformity**

Diluent: Hydrochloric acid (1 in 100)

Standard solution: 40 µg/mL of USP Quinine Sulfate RS in *Diluent*

Sample solution: Transfer the contents of one Capsule to a 250-mL volumetric flask, add 175 mL of *Diluent*, and shake by mechanical means for 30 min. Add *Diluent* to volume. Filter a portion of the mixture, discarding the first 20 mL of the filtrate.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* <851>.)

Mode: UV

Cell: 1 cm

Analytical wavelength: Maximum at about 345 nm

Blank: Water

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$, in the Capsule taken:

$$\text{Result} = (A_U / A_S) \times (C_S / C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of quinine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: Meet the requirements

IMPURITIES**ORGANIC IMPURITIES**

Standard stock solution: 6 mg/mL of USP Quinine Sulfate RS in diluted alcohol

Standard solution A: 0.06 mg/mL of USP Quinine Sulfate RS from the *Standard stock solution* in diluted alcohol

Standard solution B: 0.05 mg/mL of USP Quinone RS (corresponding to 0.06 mg/mL of the sulfate) and 0.10 mg/mL of cinchonidine (corresponding to 0.12 mg/mL of the sulfate) in diluted alcohol

Sample solution: Nominally 6 mg/mL of quinine sulfate in diluted alcohol prepared as follows. Shake the equivalent of 150 mg of quinine sulfate from the contents of Capsules with 25 mL of diluted alcohol for 10 min, and filter.

Chromatographic system

(See *Chromatography* <621>, *Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 10 µL

Developing solvent system: Chloroform, acetone, and diethylamine (50:40:10). [NOTE—The solvent chamber being used without previous equilibration.]

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Proceed as directed in *Chromatography* ⟨621⟩, *Thin-Layer Chromatography*. Allow the spots to dry, and develop the chromatogram using a solvent chamber without previous equilibration. When the solvent front has moved about 15 cm, remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by spraying with glacial acetic acid, and examine under long-wave-length UV light.

Acceptance criteria: Any spot produced by the *Sample solution* at the R_f value of a spot produced by *Standard solution B* is not greater in size or intensity than that corresponding spot. Apart from these spots and from the spot appearing at the R_f value of quinine sulfate, any additional fluorescent spot is not greater in size or intensity than the spot from *Standard solution A*. Spray the plate with potassium iodoplatinate TS. Any spot produced by the *Sample solution* is not greater in size or intensity than a corresponding spot from *Standard solution B*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Quinine Sulfate RS

USP Quininone RS

■Cinchonan-9-one, 6'-methoxy-, (8 α)-, ■TS (USP36)
 $C_{20}H_{22}N_2O_2$ 322.40

Quinine Sulfate Tablets**DEFINITION**

Quinine Sulfate Tablets contain amounts of quinine sulfate and dihydroquinine sulfate totaling NLT 90.0% and NMT 110.0% of the labeled amount of quinine sulfate, calculated as $(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O$.

IDENTIFICATION

- **A.**
Sample: Nominally 100 mg of quinine sulfate from powdered Tablets
Analysis: Shake the *Sample* well with 100 mL of dilute sulfuric acid (1 in 350), and filter.
Acceptance criteria: An appropriate dilution of the filtrate exhibits a vivid blue fluorescence. On the addition of a few drops of hydrochloric acid, the fluorescence disappears.
- **B.** The R_f value of the principal spot from the *Sample solution* corresponds to that from the *Standard solution A*, as obtained in the test for *Organic Impurities*.
- **C. IDENTIFICATION TESTS—GENERAL, Sulfate** ⟨191⟩
Sample: Nominally 20 mg of quinine sulfate from powdered Tablets
Analysis: Shake *Sample* with 10 mL of dilute hydrochloric acid (1 in 100), and filter
Acceptance criteria: The filtrate meets the requirements.
- **D.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY**Change to read:**• **PROCEDURE**

Solution A: Add 35.0 mL of methanesulfonic acid to 20.0 mL of glacial acetic acid, and dilute with water to 500 mL.

Solution B: Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.

Mobile phase: Acetonitrile, *Solution B*, *Solution A*, and water (10:2:2:86). Adjust with *Solution B* to a pH of 2.6 if the pH is found to be lower.

System suitability solution: 0.2 mg/mL each of USP Quinine Sulfate RS and dihydroquinine, dissolved in 10% of the final volume of methanol. Dilute with *Mobile phase* to volume.

Standard solution: 0.2 mg/mL of USP Quinine Sulfate RS in *Mobile phase*

Sample stock solution: Nominally 1.6 mg/mL of quinine sulfate prepared as follows. Transfer an equivalent to 160 mg of quinine sulfate from NLT 20 powdered Tablets to a 100-mL volumetric flask, add 80 mL of methanol, and shake by mechanical means for 30 min. Dilute with methanol to volume, and filter, discarding the first 10 mL of the filtrate.

Sample solution: Nominally 0.2 mg/mL of quinine sulfate in *Mobile phase* from the *Sample stock solution*

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 3.9-mm \times 30-cm; packing L1

■Flow rate: 1 mL/min■TS (USP36)

Injection volume: 50 μ L

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for quinine and dihydroquinine are 1 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 1.2 between quinine and dihydroquinine

Relative standard deviation: NMT 2.0% for the quinine peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of quinine sulfate and dihydroquinone sulfate in the portion of Tablets taken:

$$\text{Result} = [(r_{B,U} + r_{D,U}) / (r_{B,S} + r_{D,S})] \times (C_S / C_U) \times 100$$

$r_{B,U}$ = peak area response of quinine from the *Sample solution*

$r_{D,U}$ = peak area response of dihydroquinine from the *Sample solution*

$r_{B,S}$ = peak area response of quinine from the *Standard solution*

$r_{D,S}$ = peak area response of dihydroquinine from the *Standard solution*

C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of quinine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS• **DISSOLUTION** ⟨711⟩

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Detection: UV maximum at about 248 nm

Standard solution: Prepare a solution of known concentration of USP Quinine Sulfate RS in *Medium*.

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium*

Analysis: Determine the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot H_2O]$ dissolved.

Tolerances: NLT 75% (Q) of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ is dissolved.

• **UNIFORMITY OF DOSAGE UNITS (905)**

Procedure for content uniformity

Diluent: Hydrochloric acid (1 in 100)

Standard solution: 40 µg/mL of USP Quinine Sulfate RS in *Diluent*

Sample solution: Transfer the contents of one powdered Tablet to a 250-mL volumetric flask, add 175 mL of *Diluent*, and shake by mechanical means for 30 min. Add *Diluent* to volume. Filter a portion of the mixture, discarding the first 20 mL of the filtrate.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV

Cell: 1 cm

Analytical wavelength: Maximum at about 345 nm

Blank: Water

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of quinine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$, in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Quinine Sulfate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of quinine sulfate in the *Sample solution* (mg/mL)

Acceptance criteria: Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**

Standard stock solution: 6 mg/mL of USP Quinine Sulfate RS in diluted alcohol

Standard solution A: 0.06 mg/mL of USP Quinine Sulfate RS from *Standard stock solution* in diluted alcohol

Standard solution B: 0.05 mg/mL of USP Quinone RS (corresponding to 0.06 mg/mL of the sulfate), and 0.10 mg/mL of cinchonidine (corresponding to 0.12 mg/mL of the sulfate) in diluted alcohol

Sample solution: Nominally 6 mg/mL of quinine sulfate prepared as follows. Shake the equivalent of 150 mg of quinine sulfate from powdered Tablets with 25 mL of diluted alcohol for 10 min, and filter.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 10 µL

Developing solvent system: Chloroform, acetone, and diethylamine (50:40:10). [NOTE—The solvent chamber being used without previous equilibration.]

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Proceed as directed for *Chromatography* (621), *Thin-Layer Chromatography*. Allow the spots to dry, and develop the chromatogram in a solvent system until the solvent front has moved 15 cm. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by spraying with glacial acetic acid, and examine under long-wavelength UV light.

Acceptance criteria: Any spot produced by the *Sample solution* at the R_f value of a spot produced by *Standard solution B* is not greater in size or intensity than that corresponding spot. Apart from these spots and from the spot appearing at the R_f value of quinine, any additional fluorescent spot is not greater in size or intensity than the spot from *Standard solution A*. Spray the plate with potassium iodoplatinate TS. Any spot produced by the *Sample solution* is not greater in size or intensity than a corresponding spot from *Standard solution B*.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers.

Change to read:

• **USP REFERENCE STANDARDS (11)**

USP Quinine Sulfate RS

USP Quinone RS

■ Cinchon-9-one, 6'-methoxy-, (8α)-, ■ TS (USP36)
 $C_{20}H_{22}N_2O_2$ 322.40

Add the following:

• Ribavirin Capsules

DEFINITION

Ribavirin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$).

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Mobile phase: Water. Adjust with sulfuric acid to a pH of 2.5.

Standard solution: 0.025 mg/mL of USP Ribavirin RS in *Mobile phase*

Sample stock solution: Transfer an equivalent to 50 mg of ribavirin, from contents of Capsules (NLT 20), to a 100-mL volumetric flask. Add about 50 mL of *Mobile phase*, and sonicate with occasional shaking for about 20 min. Cool to room temperature, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.025 mg/mL of ribavirin in *Mobile phase* from *Sample stock solution*. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 207 nm

Column: 7.8-mm × 15-cm; 7-µm packing L17

Column temperature: 65°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.7–1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
 r_S = peak response from the *Standard solution*
 C_S = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of ribavirin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS• **DISSOLUTION** (711)

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Determine the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) dissolved by using one of the following procedures.

Procedure 1

Mobile phase: Proceed as directed in the *Assay*.

Standard solution: 22.5 µg/mL of USP Ribavirin RS in *Medium*

Sample solution: Pass the solution through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate to a 50.0-mL volumetric flask, and dilute with *Medium* to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 207 nm

Column: 7.8-mm × 30-cm; 7-µm packing L17

Column temperature: 65°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times D \times 100$$

r_U = peak area from the *Sample solution*
 r_S = peak area from the *Standard solution*
 C_S = concentration of the *Standard solution* (mg/mL)
 L = label claim (mg/Capsule)
 V = volume of *Medium*, 900 mL
 D = dilution factor of the solution under test

Procedure 2

Sulfuric acid solution: 3% sulfuric acid

Mobile phase: Water. Adjust with *Sulfuric acid solution* to a pH of 2.5.

Standard solution: 0.02 mg/mL of USP Ribavirin RS in *Medium*

Sample solution: Pass the solution through a suitable filter of 0.8-µm pore size. Transfer 5.0 mL of the filtrate

to a 50.0-mL volumetric flask, and dilute with water to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 207 nm

Column: 7.8-mm × 10-cm; 9-µm packing L17

Column temperature: 40° ± 2°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times D \times 100$$

r_U = peak area from the *Sample solution*
 r_S = peak area from the *Standard solution*
 C_S = concentration of the *Standard solution* (mg/mL)
 L = label claim (mg/Capsule)
 V = volume of *Medium*, 900 mL
 D = dilution factor of the solution under test

Tolerances: NLT 80% (Q) of the labeled amount of ribavirin ($C_8H_{12}N_4O_5$) is dissolved.

• **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

IMPURITIES• **ORGANIC IMPURITIES**

Mobile phase, Standard solution, and Chromatographic system: Proceed as directed in the *Assay*.

Sample solution: Nominally 0.5 mg/mL in *Mobile phase* prepared as follows. Transfer an amount equivalent to 50 mg of ribavirin, from contents of Capsules (NLT 20), to a 100-mL volumetric flask. Add about 50 mL of *Mobile phase*, and sonicate with occasional shaking for about 20 min. Cool to room temperature, dilute with *Mobile phase* to volume, and mix. Pass the solution through a suitable filter of 0.45-µm pore size.

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of ribose triazolole carboxylic acid and any other unknown impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of ribose triazolole carboxylic acid or any other unknown impurity from the *Sample solution*
 r_S = peak response of ribavirin from the *Standard solution*
 C_S = concentration of USP Ribavirin RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of ribavirin in the *Sample solution* (mg/mL)
 F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

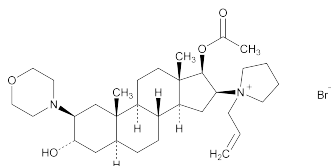
Table 1

Name	Relative Retention Time	Relative Response Factor (F)	Acceptance Criteria (%)
Ribose triazole carboxylic acid ^a	0.7	0.7	0.25
Ribavirin	1.0	—	—
Any individual unknown impurity	—	1.0	0.10
Total impurities	—	—	1.0

^a 1-β-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxylic acid.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store between 15° and 30°.
- **USP REFERENCE STANDARDS** (11)
USP Ribavirin RS_{1S} (USP36)

Rocuronium Bromide

C₃₂H₅₃BrN₂O₄ 609.68
 Pyrrolidinium, 1-[(2β,3α,5α,16β,17β)-17-(acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl]-1-(2-propenyl)-, bromide;
 1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-androstan-16β-yl)pyrrolidinium bromide, 17-acetate [119302-91-9].

DEFINITION

Rocuronium Bromide contains NLT 98.0% and NMT 102.0% of rocuronium bromide (C₃₂H₅₃BrN₂O₄), calculated on the anhydrous and 2-propanol-free or acetic acid-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197M)
- **B.** The retention time of the rocuronium bromide peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. IDENTIFICATION TESTS—GENERAL, Bromide** (191)
Sample solution: 10 mg/mL
Acceptance criteria: Meets the requirements of the silver nitrate test

ASSAY• **PROCEDURE**

Diluent: Acetonitrile and water (90:10)

Buffer: 4.53 g/L of tetramethylammonium hydroxide pentahydrate. Adjust the solution with phosphoric acid to a pH of 7.4.

Mobile phase: Acetonitrile and *Buffer* (90:10)

Standard solution: 1 mg/mL of USP Rocuronium Bromide RS in *Diluent*

Sample solution: 1 mg/mL of Rocuronium Bromide in *Diluent*

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-μm packing L3

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 5 μL

System suitability

[NOTE—The system may need equilibration for 4 h.]

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rocuronium bromide (C₃₂H₅₃BrN₂O₄) in the portion of the sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Rocuronium Bromide RS in the *Standard solution* (mg/mL)

C_U = concentration of Rocuronium Bromide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous and 2-propanol-free or acetic acid-free basis

IMPURITIES

• **HEAVY METALS, Method II** (231): NMT 10 ppm

• **RESIDUE ON IGNITION** (281): NMT 0.1%

• **ORGANIC IMPURITIES**

Diluent, Mobile phase, and Chromatographic system:
 Proceed as directed in the *Assay*.

Peak identification solution: 1 mg/mL of USP Rocuronium Peak Identification Mixture RS in *Diluent*

Standard solution: 0.01 mg/mL of USP Rocuronium Bromide RS in *Diluent*

Sample solution: 10 mg/mL of Rocuronium Bromide in *Diluent*

Run time: 2.5 times the retention time for rocuronium

System suitability

[NOTE—The system may need equilibration for 4 h.]

Sample: *Peak identification solution*

Suitability requirements

Peak-to-valley ratio: The ratio of the height of the rocuronium related compound H peak to the height of the valley between the rocuronium related compound H peak and the rocuronium peak is NLT 1.5.

Resolution: NLT 3.5 between rocuronium and rocuronium related compound C

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Rocuronium Bromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of any impurity from the *Sample solution*

r_S = peak response of rocuronium bromide from the *Standard solution*

C_S = concentration of USP Rocuronium Bromide RS in the *Standard solution* (mg/mL)

C_U = concentration of Rocuronium Bromide in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

[NOTE—Disregard any peak eluting before rocuronium bromide related compound A, and any peak with an area less than 0.5 times that of the principal peak from the *Standard solution*.]

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Rocuronium related compound A ^a	0.20	2.1	0.2
Rocuronium related compound C ^b	0.44	2.3	0.1
Rocuronium related compound F ^c	0.75	0.79	0.1
Rocuronium related compound B ^d	0.80	1.0	0.3
Rocuronium related compound D ^e	0.90	1.0	0.1
Rocuronium related compound H ^f	0.95	2.9	0.1
Rocuronium bromide	1.0	—	—
Rocuronium related compound G ^g	1.20	1.0	0.3
Rocuronium related compound E ^h	1.53	1.0	0.1
Any individual unspecified impurity	—	—	0.10
Total impurities	—	—	1.5

^a 3 α -Hydroxy-2 β -(morpholin-4-yl)-16 β -(pyrrolidin-1-yl)-5 α -androstan-17 β -yl acetate.

^b 2 β -(Morpholin-4-yl)-16 β -(pyrrolidin-1-yl)-5 α -androstan-3 α ,17 β -diol.

^c 1-[3 α ,17 β -Bis(acetyloxy)-2 β -(pyrrolidin-1-yl)-5 α -androstan-16 β -yl]-1-(prop-2-enyl)pyrrolidinium.

^d 1-[3 α ,17 β -Bis(acetyloxy)-2 β -(morpholin-4-yl)-5 α -androstan-16 β -yl]-1-(prop-2-enyl)pyrrolidinium.

^e 1-[3 α -(Acetyloxy)-17 β -hydroxy-2 β -(morpholin-4-yl)-5 α -androstan-16 β -yl]-1-(prop-2-enyl)pyrrolidinium.

^f 1-[17 β -(Acetyloxy)-2-(morpholin-4-yl)-3-oxo-5 α -androstan-1-en-16 β -yl]-1-(prop-2-enyl)pyrrolidinium.

^g 1-[3 α ,17 β -Dihydroxy-2 β -(morpholin-4-yl)-5 α -androstan-16 β -yl]-1-(prop-2-enyl)pyrrolidinium.

^h 1-[17 β -(Acetyloxy)-3 α -hydroxy-2 β -(pyrrolidin-1-yl)-5 α -androstan-16 β -yl]-1-(prop-2-enyl)pyrrolidinium.

Change to read:

• LIMIT OF 2-PROPANOL

[NOTE—Perform this test only if 2-propanol is a known organic manufacturing process impurity.]

Standard stock solution: Transfer 35.0 μ L of ethyl ether, 32.0 μ L of 2-propanol, and 19.0 μ L of methylene chloride to a 100-mL volumetric flask containing 90 mL of dimethylformamide (DMF), and dilute with DMF to volume.

Standard solution: Transfer 2.5 mL of the *Standard stock solution* to a 25-mL volumetric flask containing 20 mL of DMF, and dilute with DMF to volume.

Dilute standard solution: Transfer 1.0 mL of the *Standard solution* and 4.0 mL of water to a 20-mL headspace vial. Immediately close the vial with a cap, and mix.

Sample solution: Transfer 50 mg of Rocuronium Bromide to a 20-mL headspace vial. Dissolve in 1.0 mL of DMF. Add 4 mL of water, immediately close the vial with a cap, and mix.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.32-mm \times 60-m μ S (USP36) fused silica; coated with a 1.8- μ m layer of liquid phase G43

Temperatures

Injector: 140°

Detector: 280°

Column: See *Table 2*.

Table 2

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	8
50	20	250	8

Carrier gas: Helium with a linear velocity of 55 cm/s or nitrogen with a linear velocity of 25 cm/s

Injection type: Split ratio, 1:6

Head space autosampler

Sample equilibration temperature: 90°

Sample equilibration time: 15 min

Transfer line temperature: 140°

System suitability

Sample: *Dilute standard solution*

[NOTE—The relative retention times for ethyl ether, 2-propanol, and methylene chloride are 0.87, 1.0, and 1.08, respectively.]

Suitability requirements

Resolution: NLT 1.0 between ethyl ether and 2-propanol; NLT 1.0 between 2-propanol and methylene chloride

Relative standard deviation: NMT 10.0% for the 2-propanol peak

Analysis

Samples: *Dilute standard solution* and *Sample solution*

Calculate the percentage of 2-propanol in the portion of Rocuronium Bromide taken:

$$\text{Result} = [(r_U/r_S) \times (V \times D/W) \times 100]/F$$

r_U = peak response of any impurity from the *Sample solution*

r_S = peak response of rocuronium bromide from the *Dilute standard solution*

V = volume of 2-propanol taken to prepare the *Standard stock solution* (μ L)

D = relative density of 2-propanol, 0.786 mg/ μ L

W = weight of Rocuronium Bromide taken to prepare the *Sample solution* (mg)

F = dilution factor for the *Standard solution*, 1000

Acceptance criteria: NMT 1.0%

• LIMIT OF ACETIC ACID

[NOTE—Perform this test only if acetic acid is a known organic manufacturing process impurity.]

Mobile phase: 6.1 g of sodium perchlorate in 800 mL of water. Adjust with 1 N sulfuric acid to a pH of 2.0. Dilute to 1 L.

Standard solution: 0.2 mg/mL of glacial acetic acid in *Mobile phase*

Sample solution: 6.0 mg/mL of Rocuronium Bromide in *Mobile phase*. [NOTE—Sonication may be necessary to completely dissolve the rocuronium bromide.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm \times 15-cm; packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 μ L

System suitability

Sample: *Standard solution*

[NOTE—The retention time of acetic acid is about 3.8 min.]

Suitability requirements

Column efficiency: NLT 5000 theoretical plates

Tailing factor: NMT 1.8

Relative standard deviation: NMT 5.0% for three injections

Analysis**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of acetic acid in the portion of Rocuronium Bromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response for acetic acid from the *Sample solution* r_S = peak response for acetic acid from the *Standard solution* C_S = concentration of acetic acid in the *Standard solution* (mg/mL) C_U = concentration of Rocuronium Bromide in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 5.0%

SPECIFIC TESTS

- **WATER DETERMINATION**, *Method 1c* (921): NMT 4.0%

- **PH** (791)

Sample solution: 10 mg/mL

Acceptance criteria: 7.0–9.5

- **OPTICAL ROTATION**, *Specific Rotation* (781S)

Sample solution: 10 mg/mL in 0.05 M hydrochloric acid

Acceptance criteria: 28.5°–32.0°, measured on the anhydrous and solvent-free basis at 20°

- **COLOR AND ACHROMICITY** (631)

Reference solution: Mix 33 mL of *Matching Fluid G* and 67 mL of water.

Sample solution: 10 mg/mL of Rocuronium Bromide in water

Analysis: Proceed as directed for *Color and Achromicity* (631).Acceptance criteria: The *Sample solution* is not more intensely colored than the *Reference solution*.**ADDITIONAL REQUIREMENTS****Change to read:**

- **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light and moisture. Store ■ in the freezer. ■1S (USP36) If the article contains acetic acid, store it between 2° and 8°.
- **USP REFERENCE STANDARDS** (11)
USP Rocuronium Bromide RS
USP Rocuronium Peak Identification Mixture RS
Mixture of approximately 0.2% to 0.4% each of rocuronium related compound A, rocuronium related compound B, rocuronium related compound C, rocuronium related compound D, rocuronium related compound E, rocuronium related compound F, rocuronium related compound G, and rocuronium related compound H in a matrix of rocuronium bromide.

Salicylic Acid Plaster**DEFINITION**

Salicylic Acid Plaster is a uniform mixture of Salicylic Acid in a suitable base, spread on paper, cotton cloth, or other suitable backing material. The plaster mass contains NLT 90.0% and NMT 110.0% of the labeled amount of salicylic acid ($C_7H_6O_3$).

IDENTIFICATION**Add the following:**

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.■1S (USP36)

ASSAY**Change to read:**• **PROCEDURE**■**Solution A:** Methanol and 2% (v/v) phosphoric acid in water (1:1)**Solution B:** Methanol**Mobile phase:** See *Table 1*.**Table 1**

Time (min)	Solution A (%)	Solution B (%)	Flow Rate (mL/min)
0	100	0	1.0
5.5	100	0	1.0
5.6	0	100	2.0
7.1	0	100	2.0
7.2	100	0	2.0
9.4	100	0	2.0
9.5	100	0	1.0
10.0	100	0	1.0

Diluent: Tetrahydrofuran and hydrochloric acid (99:1)**Standard solution:** 0.2 mg/mL of USP Salicylic Acid RS prepared as follows. Transfer USP Salicylic Acid RS to a suitable volumetric flask, and add *Diluent* equivalent to 12.5% of the final volume to dissolve. Dilute with *Solution A* to volume. Protect from light.**Sample solution:** Transfer Plaster (scrape it from the fabric if needed), equivalent to 40 mg of salicylic acid, to a 200-mL volumetric flask, and add 25 mL of *Diluent* to dissolve. Sonicate if necessary to facilitate dissolution. Dilute with *Solution A* to volume. Mix, filter, and discard the first few mL. Protect from light.**Chromatographic system**(See *Chromatography* (621), *System Suitability*.)**Mode:** LC**Detector:** UV 306 nm**Column:** 4.6-mm × 15-cm; 5-μm packing L11**Injection volume:** 10 μL**System suitability****Sample:** *Standard solution***Suitability requirements****Tailing factor:** NMT 2.0**Relative standard deviation:** NMT 2.0%**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of salicylic acid ($C_7H_6O_3$) in the portion of Plaster taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak area from the *Sample solution* r_S = peak area from the *Standard solution* C_S = concentration of USP Salicylic Acid RS in the *Standard solution* (mg/mL) C_U = nominal concentration of salicylic acid in the *Sample solution* (mg/mL)■1S (USP36)

Acceptance criteria: 90.0%–110.0%

ADDITIONAL REQUIREMENTS

Change to read:

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. ■Store between 20° and 25°. ■1S (USP36)

Add the following:

- **USP REFERENCE STANDARDS (11)**
USP Salicylic Acid RS ■1S (USP36)

Sulfasalazine Delayed-Release Tablets

DEFINITION

Sulfasalazine Delayed-Release Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of sulfasalazine ($C_{18}H_{14}N_4O_5S$).

IDENTIFICATION

Add the following:

- **A.**
Standard solution and Sample solution: Proceed as directed in the Assay.
Acceptance criteria: The visible absorption spectrum of the *Sample solution* corresponds to that of the *Standard solution*, as prepared in the Assay. ■1S (USP36)

ASSAY

PROCEDURE

Standard solution: 7.5 µg/mL of USP Sulfasalazine RS in the same medium as the *Sample solution*

Sample stock solution: Nominally 1.5 mg/mL of sulfasalazine prepared as follows. Dissolve an appropriate amount of sulfasalazine from finely powdered Tablets (NLT 20) in 0.1 N sodium hydroxide in a suitable volumetric flask.

Sample solution: Nominally 7.5 µg/mL of sulfasalazine prepared as follows. Transfer 5.0 mL of the *Sample stock solution* to a 1000-mL volumetric flask containing 750 mL of water. Mix, add 20.0 mL of 0.1 N acetic acid, and dilute with water to volume.

Instrumental conditions

(See *Spectrophotometry and Light-Scattering* (851).)

Mode: UV

Analytical wavelength: Maximum at about 359 nm

Blank: Water

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*. Concomitantly determine the absorbances of the *Samples*.

Calculate the percentage of the labeled amount of sulfasalazine ($C_{18}H_{14}N_4O_5S$) in the portion of Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Sulfasalazine RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of sulfasalazine in the *Sample solution* (µg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION (711):** Proceed as directed in the *Procedure* for *Method B* in *Apparatus 1* and *Apparatus 2*, *Delayed-Release Dosage Forms*.

Acid stage

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 120 min

At the end of 120 min, determine the amount of sulfasalazine ($C_{18}H_{14}N_4O_5S$) dissolved by using the following method.

Mobile phase: Isopropanol, acetonitrile, water, and glacial acetic acid (11: 7: 22: 0.4)

Standard solution: 55.6 µg/mL of USP Sulfasalazine RS in 0.1 N sodium hydroxide

Sample solution: Pass about 7 mL of the solution under test through a membrane filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; ■5-µm ■1S (USP36) packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[NOTE—The retention time for sulfasalazine is about 7.7 min.]

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of sulfasalazine ($C_{18}H_{14}N_4O_5S$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Sulfasalazine RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NMT 10% of the labeled amount of sulfasalazine ($C_{18}H_{14}N_4O_5S$) is dissolved.

Buffer stage

Medium: pH 7.5 phosphate buffer; 900 mL

Apparatus 1: 100 rpm

Time: 60 min

At the end of 60 min, determine the amount of sulfasalazine ($C_{18}H_{14}N_4O_5S$) dissolved by using the chromatographic method as described in *Acid stage*.

Tolerances: NLT 85% (Q) of the labeled amount of sulfasalazine ($C_{18}H_{14}N_4O_5S$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

SPECIFIC TESTS

Delete the following:

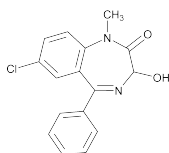
- **OTHER REQUIREMENTS:** Tablets respond to the *Identification* test and meet the requirements for *Uniformity of dosage units* and *Assay* under *Sulfasalazine Tablets*. ■1S (USP36)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers.

- **USP REFERENCE STANDARDS** (11)
USP Sulfasalazine RS

Temazepam



$C_{16}H_{13}ClN_2O_2$ 300.74
2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-;
7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one [846-50-4].

DEFINITION

Temazepam contains NLT 98.0% and NMT 102.0% of temazepam ($C_{16}H_{13}ClN_2O_2$), calculated on the dried basis. **[CAUTION]**—Temazepam is a potent sedative: its powder should not be inhaled.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197K)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY

PROCEDURE

Buffer: 2.7 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (47:53)

Diluent: Methanol and water (90:10)

Standard solution: 0.2 mg/mL of USP Temazepam RS in *Diluent*

Sample solution: 0.2 mg/mL of Temazepam in *Diluent*

Chromatographic system
(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4-mm × 25-cm; 5-μm packing L16

Flow rate: 2 mL/min

Injection volume: 10 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 800 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of temazepam ($C_{16}H_{13}ClN_2O_2$) in the portion of Temazepam taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Temazepam RS in the *Standard solution* (mg/mL)

C_U = concentration of Temazepam in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%

Change to read:

- **HEAVY METALS**, *Method II* (231): $\text{NMT}_{15} \text{ (USP36)}$ 20 μg/g

Change to read:

ORGANIC IMPURITIES

Solution A: 3.9 g/L of ammonium acetate in water

Solution B: Acetonitrile

Diluent: Acetonitrile and *Solution A* (30:70)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	70	30
13	70	30
25	30	70
28	30	70
33	70	30
35	70	30

Standard stock solution 1: 0.1 mg/mL of USP

Temazepam RS prepared as follows. Dissolve the Standard in acetonitrile using 30% of the final volume, and dilute with *Solution A* to volume.

Standard stock solution 2: 0.1 mg/mL each of USP

Temazepam Related Compound A RS, USP Temazepam Related Compound F RS, and USP Temazepam Related Compound G RS prepared as follows. Dissolve the Standards in acetonitrile using 30% of the final volume, and dilute with *Solution A* to volume. [NOTE—Temazepam related compound A is used in *Standard stock solution 2* for identification purposes only.]

Standard solution: 5 μg/mL each of USP Temazepam

RS, USP Temazepam Related Compound A RS, USP Temazepam Related Compound F RS, and USP Temazepam Related Compound G RS in *Diluent*, from *Standard stock solution 1* and *Standard stock solution 2*

Sensitivity solution: 0.2 μg/mL of USP Temazepam RS in *Diluent* from *Standard stock solution 1*

Sample solution: 1 mg/mL of Temazepam prepared as follows. Dissolve in acetonitrile using 30% of the final volume, and dilute with *Solution A* to volume.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 7.5-cm; 3.5-μm packing L1

Flow rate: 1 mL/min

Injection volume: 20 μL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Resolution: NLT 1.5 between temazepam related compound F and temazepam; NLT 1.5 between temazepam and temazepam related compound G, *Standard solution*

Relative standard deviation: NMT 5.0% for temazepam, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Temazepam taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

- r_U = peak response of each impurity from the *Sample solution*
 r_S = peak response of temazepam from the *Standard solution*
 C_S = concentration of USP Temazepam RS in the *Standard solution* (mg/mL)
 C_U = concentration of Temazepam in the *Sample solution* (mg/mL)
 F = relative response factor (see Table 2)
Acceptance criteria: See Table 2. [NOTE—The reporting limit is 0.02% for temazepam related compound A, and 0.05% for all other impurities.]

Table 2

Compound	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Oxazepam ^a	0.54	1.0	0.2
Methylnordazepam N-oxide ^b	0.63	1.5	0.2
Temazepam related compound F ^c	0.83	0.65	0.2
Temazepam	1.0	—	—
Temazepam related compound G ^d	1.3	0.68	0.2
O-Methyl temazepam ^e	1.6	1.0	0.2
O-Acetyl temazepam ^f	2.0	1.0	0.2
Temazepam related compound A ^g	2.6	1.2	0.05
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.5

^a 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one.

^b 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide.

^c 7-Chloro-1-methyl-5-phenyl-4,5-dihydro-1H-1,4-benzodiazepine-2,3-dione.

^d 7-Chloro-1,4-dimethyl-5-phenyl-4,5-dihydro-1H-1,4-benzodiazepine-2,3-dione.

^e 7-Chloro-1,3-dihydro-3-methoxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

^f 7-Chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl acetate.

^g 5-Chloro-2-methylaminobenzophenone.

■_{1S} (USP36)

SPECIFIC TESTS

• LOSS ON DRYING (731)

Analysis: Dry a sample at 105° for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers.

Change to read:

• USP REFERENCE STANDARDS (11)

USP Temazepam RS

■ USP Temazepam Related Compound A RS

5-Chloro-2-methylaminobenzophenone.

C₁₄H₁₂ClNO 245.70

USP Temazepam Related Compound F RS

7-Chloro-1-methyl-5-phenyl-4,5-dihydro-1H-1,4-benzodiazepine-2,3-dione.

C₁₆H₁₃ClN₂O₂ 300.74

USP Temazepam Related Compound G RS

7-Chloro-1,4-dimethyl-5-phenyl-4,5-dihydro-1H-1,4-benzodiazepine-2,3-dione.

C₁₇H₁₅ClN₂O₂ 314.77 ■_{1S} (USP36)

Thioridazine Hydrochloride Tablets

DEFINITION

Thioridazine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of thioridazine hydrochloride (C₂₁H₂₆N₂S₂ · HCl).

Throughout the following procedures, protect samples, the Reference Standard, and the solutions containing them by conducting the procedures without delay, under subdued light, or by using low-actinic glassware.

IDENTIFICATION

Change to read:

- **A.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay. ■_{1S} (USP36)

ASSAY

Change to read:

• PROCEDURE

Mobile phase: Acetonitrile, water, and triethylamine (850:150:1)

System suitability solution: 0.1 mg/mL of ■ USP Mesoridazine Besylate RS ■_{1S} (USP36) and 0.11 mg/mL of USP Thioridazine Hydrochloride RS in methanol

Standard solution: 125 µg/mL of USP Thioridazine Hydrochloride RS in methanol. Sonication may be used to aid dissolution.

Sample stock solution: Nominally 1.0 mg/mL prepared as follows. Weigh and finely powder NLT 20 Tablets. Transfer a weighed portion of the powder, equivalent to 100 mg of thioridazine hydrochloride, to a 100-mL volumetric flask. Add 80 mL of methanol, and shake by mechanical means for 30 min. Dilute with methanol to volume, and sonicate for 45 min with intermittent shaking. Allow the undissolved solids to settle, and filter, discarding the first 20 mL of the filtrate.

Sample solution: 125 µg/mL in methanol from a portion of filtrate from the *Sample stock solution*. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 265 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 2.5 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

■ [NOTE—The relative retention times for mesoridazine and thioridazine are 0.44 and 1.0, respectively.] ■_{1S} (USP36)

Suitability requirements

Resolution: NLT 1.0 between mesoridazine and thioridazine, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*
 Calculate the percentage of the labeled amount of thioridazine hydrochloride (C₂₁H₂₆N₂S₂ · HCl) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of thioridazine from the *Sample solution*

- r_s = peak response of thioridazine from the *Standard solution*
 C_s = concentration of USP Thioridazine Hydrochloride RS in the *Standard solution* ($\mu\text{g/mL}$)
 C_U = nominal concentration of thioridazine hydrochloride in the *Sample solution* ($\mu\text{g/mL}$)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** (711)
Medium: 0.01 N hydrochloric acid; 1000 mL
Apparatus 2: 75 rpm
Time: 60 min
Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary, to a concentration similar to that of the *Standard solution*.
Standard solution: USP Thioridazine Hydrochloride RS in *Medium* at a known concentration
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* (851).)
Mode: UV
Analytical wavelength: 262 nm
Blank: *Medium*
Tolerances: NLT 75% (Q) of the labeled amount of thioridazine hydrochloride ($\text{C}_{21}\text{H}_{26}\text{N}_2\text{S}_2 \cdot \text{HCl}$) is dissolved.
- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

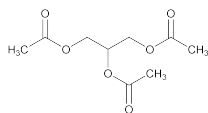
ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Change to read:

- **USP REFERENCE STANDARDS** (11)
■ USP Mesoridazine Besylate RS ■_{1S} (USP36)
USP Thioridazine Hydrochloride RS

Triacetin



$\text{C}_9\text{H}_{14}\text{O}_6$ 218.21
1,2,3-Propanetriol triacetate;
Triacetin;
Glyceryl triacetate [102-76-1].

DEFINITION

Triacetin contains NLT 97.0% and NMT 100.5% of $\text{C}_9\text{H}_{14}\text{O}_6$, calculated on the anhydrous basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** (197F)

Change to read:

- **B.**
Sample solution: ■ Dilute the solution prepared in the *Assay* to 10 mg/mL in 0.5 N alcoholic potassium hydroxide. ■_{1S} (USP36)
Acceptance criteria: The solution meets the requirements of *Identification Tests—General* (191), *Acetate*.

ASSAY

• PROCEDURE

Sample: 1 g

Titrimetric system

(See *Titrimetry* (541), *Residual Titrations*.)

Mode: Direct titration

Titrant: 0.5 N alcoholic potassium hydroxide VS

Back-titrant: 0.5 N hydrochloric acid VS

Endpoint detection: Visual

Analysis: Transfer the *Sample* to a 250-mL boiling flask. Add 50.0 mL of *Titrant*, connect the flask to a water-jacketed condenser, and reflux on a steam bath for 45 min, swirling frequently. Cool, and add 5 drops of phenolphthalein TS. Titrate the excess alkali with *Back-titrant*. Perform a blank determination. Each mL of *Titrant* is equivalent to 36.37 mg of triacetin ($\text{C}_9\text{H}_{14}\text{O}_6$).

Acceptance criteria: 97.0%–100.5% on the anhydrous basis

SPECIFIC TESTS

- **SPECIFIC GRAVITY** (841): 1.152–1.158
- **REFRACTIVE INDEX** (831): 1.429–1.430

Change to read:

• ACIDITY

Sample: 25 g

Analysis: Dilute the *Sample* with 50 mL of neutralized alcohol, add 5 drops of phenolphthalein TS, and ■ add 1.0 mL of 0.020 N sodium hydroxide. ■_{1S} (USP36)

Acceptance criteria: ■ The pink color of the mixture persists for 15 s. ■_{1S} (USP36)

- **WATER DETERMINATION, Method I** (921): NMT 0.2%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS** (11)
USP Triacetin RS

Valproate Sodium Injection

DEFINITION

Valproate Sodium Injection is a sterile aqueous solution of sodium valproate, formed from the interaction of Valproic Acid and Sodium Hydroxide, in Water for Injection, and one or more suitable buffering or sequestering agents. It contains NLT 90.0% and NMT 110.0% of the labeled amount of valproic acid ($\text{C}_8\text{H}_{16}\text{O}_2$). It contains no antimicrobial agents.

IDENTIFICATION

Change to read:

- **A.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■_{1S} (USP36)
- **B. IDENTIFICATION TESTS—GENERAL, Sodium** (191): Meets the requirements

ASSAY

Change to read:

• PROCEDURE

■ **Buffer:** 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and Buffer (45:55)

Diluent: Acetonitrile and water (45:55)

System suitability solution: 0.5 mg/mL of USP Valproic Acid RS and 50 µg/mL of USP Valproic Acid Related Compound B RS in Diluent

Standard solution: 0.5 mg/mL of USP Valproic Acid RS in Diluent

Sample solution: Nominally 0.5 mg/mL of valproic acid in water from a suitable volume of Injection

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: System suitability solution and Standard solution

[NOTE—The relative retention times for valproic acid related compound B and valproic acid are 0.90 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between valproic acid related compound B and valproic acid, System suitability solution

Tailing factor: NMT 1.5, Standard solution

Relative standard deviation: NMT 1.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of valproic acid (C₈H₁₆O₂) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)

C_U = nominal concentration of valproic acid in the Sample solution (mg/mL) ■1S (USP36)

Acceptance criteria: 90.0%–110.0%

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST** (85): NMT 23 USP Endotoxin Units/mL of Injection
- **STERILITY TESTS** (71): Meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined*, *Membrane Filtration*

Change to read:

- **PARTICULATE MATTER IN INJECTIONS** (788): Meets the requirements for small-volume ■parenterals ■1S (USP36)
- **pH** (791): 7.0–9.0
- **OTHER REQUIREMENTS:** Meets the requirements in *Injections* (1)

ADDITIONAL REQUIREMENTS

Change to read:

- **PACKAGING AND STORAGE:** Preserve in single-dose containers as described in *Injections* (1), *Containers for Injection*, preferably of Type I glass. Store at controlled room temperature. ■1S (USP36)

Change to read:

- **LABELING:** It states the name and quantity of any buffering or sequestering agent used. ■It states that it is intended for use by intravenous infusion only. ■1S (USP36)

Change to read:

• USP REFERENCE STANDARDS (11)

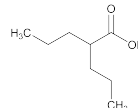
USP Endotoxin RS

USP Valproic Acid RS

■USP Valproic Acid Related Compound B RS (2RS)-2-(1-Methylethyl)pentanoic acid.

C₈H₁₆O₂ 144.21 ■1S (USP36)

Valproic Acid



C₈H₁₆O₂

144.21

Pentanoic acid, 2-propyl-;
Propylvaleric acid [99-66-1].

DEFINITION

Valproic Acid contains NLT 98.0% and NMT 102.0% of valproic acid (C₈H₁₆O₂), calculated on the anhydrous basis.

IDENTIFICATION

• A. INFRARED ABSORPTION (197F)

- **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

Change to read:

• PROCEDURE

■**Buffer:** 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and Buffer (50:50)

System suitability solution: 50 µg/mL of USP Valproic Acid Related Compound B RS and 0.5 mg/mL of USP Valproic Acid RS in Mobile phase

Standard solution: 0.5 mg/mL of USP Valproic Acid RS in Mobile phase

Sample solution: 0.5 mg/mL of Valproic Acid in Mobile phase

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: System suitability solution and Standard solution

Suitability requirements

Resolution: NLT 2.0 between valproic acid related compound B and valproic acid, System suitability solution

Tailing factor: NMT 1.5, Standard solution

Relative standard deviation: NMT 1.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of valproic acid (C₈H₁₆O₂) in the portion of Valproic Acid taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the Sample solution

r_s = peak response from the *Standard solution*
 C_s = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
 C_u = concentration of Valproic Acid in the *Sample solution* (mg/mL) \blacksquare 1S (USP36)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **RESIDUE ON IGNITION** <281>: NMT 0.1%
- **HEAVY METALS, Method II** <231>: NMT 20 ppm
- **ORGANIC IMPURITIES**

System suitability solution: 0.1 μ L/mL of USP Valproic Acid Related Compound A RS and 1.0 μ L/mL each of butyric acid and valeric acid, in Valproic Acid

Sample solution: Valproic Acid

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.32-mm \times 60-m; coated with a 0.3- μ m film of phase G25

Carrier gas: Helium

Flow rate: 150 mL/min

Injection volume: 0.5 μ L

Injection type: Split flow ratio of 100:1

Temperature

Injection port: 240°

Detector: 260°

Column: See Table 1.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
145	0	145	48
145	5	190	—

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for butyric acid, valeric acid, valproic acid, and valproic acid related compound A are 0.38, 0.52, 1.0, and 1.64, respectively.]

Suitability requirements

Resolution: NLT 23.0 between butyric acid and valeric acid

Column efficiency: NLT 100,000 theoretical plates for valeric acid

Tailing factor: NMT 1.5 for valeric acid

Retention time: The related compound A peak must elute between 41 and 50 min.

Peak area: The related compound A peak area must be NLT 0.01% relative to the valproic acid peak area.

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Valproic Acid ($C_8H_{16}O_2$) taken:

$$\text{Result} = (r_u/r_T) \times 100$$

r_u = peak response for each impurity

r_T = sum of the responses for all the peaks

Acceptance criteria

Individual impurities: NMT 0.1%

Total impurities: NMT 0.3%

SPECIFIC TESTS

- **WATER DETERMINATION, Method I** <921>: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight glass, stainless steel, or polyethylene (HDPE) containers.

Change to read:

• USP REFERENCE STANDARDS <11>

USP Valproic Acid RS

USP Valproic Acid Related Compound A RS

Diallylacetic acid.

$C_8H_{12}O_2$ 140.18

■ USP Valproic Acid Related Compound B RS

(2*RS*)-2-(1-Methylethyl)pentanoic acid.

$C_8H_{16}O_2$ 144.21 \blacksquare 1S (USP36)

Valproic Acid Capsules

DEFINITION

Valproic Acid Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of valproic acid ($C_8H_{16}O_2$).

IDENTIFICATION

Change to read:

- **A.** ■ The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. \blacksquare 1S (USP36)

• B.

Sample: Equivalent to 250 mg of valproic acid

Analysis: Place the *Sample* in a separator, add 20 mL of 1 N sodium hydroxide, shake, and allow the layers to separate. Transfer the aqueous layer to a second separator, add 4 mL of hydrochloric acid, mix, and extract with 40 mL of *n*-heptane. Filter the *n*-heptane layer through glass wool into a beaker, and evaporate the solvent completely on a steam bath with the aid of a current of air. Transfer 2 drops of the residue to a test tube containing 0.5 mL each of potassium iodide solution (1 in 50) and potassium iodate solution (1 in 25), and mix.

Acceptance criteria: A yellow color is produced.

ASSAY

Change to read:

• PROCEDURE

■ **Buffer:** 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (45:55)

Diluent: Acetonitrile and water (45:55)

System suitability solution: 0.5 mg/mL of USP Valproic Acid RS and 50 μ g/mL of USP Valproic Acid Related Compound B RS in *Diluent*

Standard solution: 0.5 mg/mL of USP Valproic Acid RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of valproic acid in *Diluent*, prepared as follows. Transfer a weighed amount of Capsule contents (NLT 20) to an appropriate volumetric flask, and dilute with *Diluent* to volume. Sonicate the resulting solution for 5 min. Alternatively, stir the resulting solution for 1 h. Centrifuge a portion of the solution for about 10 min.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm \times 15.0-cm; 5- μ m packing L7

Flow rate: 1 mL/min

Injection volume: 20 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—The relative retention times for valproic acid related compound B and valproic acid are 0.90 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between valproic acid related compound B and valproic acid, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of valproic acid in the *Sample solution* (mg/mL) ■1S (USP36)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• DISSOLUTION (711)

Medium: 5 mg/mL of sodium lauryl sulfate in simulated intestinal fluid TS (prepared without the enzyme and with monobasic sodium phosphate instead of monobasic potassium phosphate), adjusted with 5 M sodium hydroxide to a pH of 7.5; 900 mL

Apparatus 2: 50 rpm

Time: 60 min

■**Internal standard solution:** 5 mg/mL of biphenyl in *n*-heptane

Standard stock solution: ($L/900$) mg/mL of USP Valproic Acid RS in *Medium*, where L is the label claim, in mg/Capsule

Standard solution: ($L/450$) mg/mL of USP Valproic Acid RS in solution from *Standard stock solution*, where L is the label claim, in mg/Capsule, prepared as follows. Transfer 10.0 mL of the *Standard stock solution* to a suitable container, add 3.0 g of sodium chloride, and mix on a vortex mixer for 5 min. Add 1 mL of 6 N hydrochloric acid and 5.0 mL of the *Internal standard solution*, and shake for 2 min. Allow the phases to separate, remove the *n*-heptane layer, and filter.

Sample solution: Nominally ($L/450$) mg/mL of valproic acid in solution, where L is the label claim, in mg/Capsule, prepared as follows. Transfer 10.0 mL of the solution under test to a suitable container, add 3.0 g of sodium chloride, and mix on a vortex mixer for 5 min. Add 1 mL of 6 N hydrochloric acid and 5.0 mL of the *Internal standard solution*, and shake for 2 min. Allow the phases to separate, remove the *n*-heptane layer, and filter.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 2-mm × 1.8-m glass; packed with 10% phase G34 on 80- to 100-mesh support S1A

Temperatures

Column: 150°

Injection port: 250°

Detector: 250°

Carrier gas: Dry helium

Flow rate: 40 mL/min

Injection volume: 2 µL

System suitability

[NOTE—The relative retention times for valproic acid and biphenyl are 0.5 and 1.0, respectively.]

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 3.0 between valproic acid and biphenyl

Relative standard deviation: NMT 2% ■1S (USP36)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved:

$$\text{Result} = (R_U/R_S) \times C_S \times (V/L) \times 100$$

R_U = peak response ratio of valproic acid to the internal standard from the *Sample solution*

R_S = peak response ratio of valproic acid to the internal standard from the *Standard solution*

C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 85% (Q) of valproic acid ($C_8H_{16}O_2$) is dissolved.

Change to read:

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements ■1S (USP36)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

Change to read:

- **USP REFERENCE STANDARDS (11)**

USP Valproic Acid RS

■USP Valproic Acid Related Compound B RS (2RS)-2-(1-Methylethyl)pentanoic acid.

$C_8H_{16}O_2$ 144.21 ■1S (USP36)

Valproic Acid Oral Solution

DEFINITION

Valproic Acid Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of valproic acid ($C_8H_{16}O_2$). It is prepared with the aid of Sodium Hydroxide.

IDENTIFICATION

Change to read:

- **A.** ■The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*. ■1S (USP36)

- **B.**

Sample: Volume of Oral Solution equivalent to 250 mg of valproic acid

Analysis: Place the *Sample* into a separator, add 40 mL of water and 2 mL of hydrochloric acid, mix, and extract with 40 mL of *n*-heptane. Filter the *n*-heptane layer through glass wool into a beaker, and evaporate the solvent completely on a steam bath with the aid of a current of air. Transfer 2 drops of the residue to a test tube containing 0.5 mL each of potassium iodide solution (1 in 50) and potassium iodate solution (1 in 25).

Acceptance criteria: A yellow color is produced.

ASSAY

Change to read:

• PROCEDURE

Buffer: 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and Buffer (45:55)

Diluent: Acetonitrile and water (45:55)

System suitability solution: 0.5 mg/mL of USP Valproic Acid RS and 50 µg/mL of USP Valproic Acid Related Compound B RS in Diluent

Standard solution: 0.5 mg/mL of USP Valproic Acid RS in Diluent

Sample solution: Nominally 0.5 mg/mL of valproic acid in Diluent from a suitable volume of Oral Solution

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15.0-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: System suitability solution and Standard solution

[NOTE—The relative retention times for valproic acid related compound B and valproic acid are 0.90 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between valproic acid related compound B and valproic acid, System suitability solution

Tailing factor: NMT 1.5, Standard solution

Relative standard deviation: NMT 1.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of valproic acid (C₈H₁₆O₂) in the portion of Oral Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)

C_U = nominal concentration of valproic acid in the Sample solution (mg/mL) 115 (USP36)

Acceptance criteria: 90.0%–110.0%

SPECIFIC TESTS

- **pH** <791>: 7.0–8.0

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

• USP REFERENCE STANDARDS <11>

USP Valproic Acid RS

■ USP Valproic Acid Related Compound B RS
(2*RS*)-2-(1-Methylethyl)pentanoic acid.
C₈H₁₆O₂ 144.21 115 (USP36)

Venlafaxine Hydrochloride Extended-Release Capsules

DEFINITION

Venlafaxine Hydrochloride Extended-Release Capsules contain an amount of Venlafaxine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of venlafaxine (C₁₇H₂₇NO₂).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** <197U>

Wavelength range: 250–310 nm

- **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

• PROCEDURE

Mobile phase: Acetonitrile, triethylamine, and water (250:4:750). Adjust with phosphoric acid to a pH of 3.5.

Standard solution: 0.25 mg/mL of USP Venlafaxine Hydrochloride RS in Mobile phase

Sample stock solution: Nominally 1.0 mg/mL of venlafaxine (from the contents of NLT 10 Capsules) prepared as follows. Transfer a weighed quantity of Capsule contents to a suitable volumetric flask. Add 8% of the flask volume of acetonitrile, and shake for 40 min. Add 50% of flask volume of Mobile phase, and shake for an additional 20 min. Dilute with Mobile phase to volume. Pass a portion through a suitable filter of 0.45-µm pore size.

Sample solution: 0.25 mg/mL of venlafaxine (using the filtrate from the Sample stock solution) in Mobile phase

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 1.5 times the retention time of venlafaxine

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of venlafaxine (C₁₇H₂₇NO₂) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)

C_U = nominal concentration of venlafaxine in the Sample solution (mg/mL)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION <711>

Test 1

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Times: 3, 6, 16, and 24 h

Mobile phase: Acetonitrile, triethylamine, and water (450:4:550). Adjust with phosphoric acid to a pH of 3.5.

Standard stock solution: 0.1 mg/mL of USP Venlafaxine Hydrochloride RS in water

Standard solution: 0.05 mg/mL of USP Venlafaxine Hydrochloride RS in acetonitrile, from the *Standard stock solution*

Sample ^{stock} solution: (RB 1-Oct-2012) Pass a portion of the solution under test through a suitable filter.

Sample solution: *Sample stock solution* and acetonitrile (50:50) (RB 1-Oct-2012)

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 274 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Flow rate: 1 mL/min

Injection volume: 60 μL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in the *Medium* (mg/mL) after time point i :

$$\bullet \text{Result}_i = (r_U/r_S) \times C_S \times D \times (M_{r1}/M_{r2}) \bullet \text{ (RB 1-Oct-2012)}$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*, 2 (RB 1-Oct-2012)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times (V - (3 \times V_S))] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See *Table 1*.

Table 1

Time Point, i	Time (h)	Amount Dissolved
1	3	NMT 40%
2	6	35%–60%
3	16	60%–85%
4	24	NLT 75%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* <711>.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 2, 4, 8, 12, and 20 h

Capsule correction solution: Dissolve 6 empty Capsule shells in 900 mL of water.

Blank: Dilute 150 mL of *Capsule correction solution* with water to 900 mL.

Standard solution: ($L/900$) mg/mL of USP Venlafaxine Hydrochloride RS, where L is the label claim, in mg/Capsule, prepared as follows. To a weighed amount of the standard equivalent to the sample claim, add *Capsule correction solution* to fill 17% of final flask volume. Dilute with water to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Instrumental conditions

Mode: UV

Detector: 274 nm

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—If necessary, the volume of *Medium* may be corrected for volumes removed from any previous sample time points.]

Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in *Medium* (mg/mL) after time point i :

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_i = \{[C_i \times (V - ([i-1] \times V_S))] + [(C_{i-1} + C_{i-2} + \dots + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See Table 2.

Table 2

Time Point, <i>i</i>	Time (h)	Amount Dissolved
1	2	10%–30%
2	4	33%–53%
3	8	58%–78%
4	12	68%–88%
5	20	NLT 80%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution <711>.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 4, 8, and 16 h

Buffer: Dissolve 1.4 g of monobasic potassium phosphate (RB 1-Oct-2012) in 1 L of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and Buffer (35:65)

Standard stock solution: 0.9 mg/mL of USP Venlafaxine Hydrochloride RS in Medium

Standard solution: (L/750) mg/mL of USP Venlafaxine Hydrochloride RS in Medium from the Standard stock solution, where L is the label claim, in mg/Capsule. Pass a portion through a suitable filter of 0.45-μm pore size.

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh Medium. (RB 1-Oct-2012) Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-μm packing L1

Flow rate: 1 mL/min

Column temperature: 30°

Injection volume: 10 μL

Run time: 2 times the retention time of venlafaxine

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in Medium (mg/mL) after time point *i*:

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times V] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in Medium in the portion of sample withdrawn at time point *i* (mg/mL)

V = volume of Medium, 900 mL

V_S = volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)

L = label claim (mg/Capsule)

Tolerances: See Table 3.

Table 3

Time Point, <i>i</i>	Time (h)	Amount Dissolved
1	4	35%–55%
2	8	65%–90%
3	16	NLT 85%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution <711>.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 2, 4, 8, 12 and 20 h

Solution A: Dilute 10 mL of phosphoric acid with water to 100 mL.

Buffer: 11.4 g/L of ammonium dihydrogen phosphate in water

Mobile phase: Acetonitrile and Buffer (35:65). Adjust with Solution A to a pH of 4.4.

Standard stock solution: 0.24 mg/mL of USP Venlafaxine Hydrochloride RS in Medium. Sonication may be used to aid in dissolution.

Standard solution: See Table 4 for the concentration of USP Venlafaxine Hydrochloride RS in Medium from the Standard stock solution. Using a glass syringe, pass a portion through a suitable filter of 0.45-μm pore size.

Table 4

Label Claim (L)	Standard Solution (mg/mL)
37.5	0.05
75	0.1
150	0.1

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh Medium. For Capsules that are labeled to contain 150 mg of venlafaxine, dilute this solution with an equal volume of Medium. Using a glass syringe, pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 25-cm; 5-μm packing L7
Flow rate: 1.2 mL/min
Injection volume: 20 μL
Run time: 2 times the retention time of venlafaxine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
 Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in *Medium* (mg/mL) after time point i :

$$\text{Result}_i = (r_U/r_S) \times C_S \times D \times (M_{r1}/M_{r2})$$

r_U = peak response from the *Sample solution*
 r_S = peak response from the *Standard solution*
 C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)
 D = dilution factor for the *Sample solution*, 2 for Capsules labeled to contain 150 mg of venlafaxine; 1 for Capsules labeled to contain 37.5 or 75 mg of venlafaxine
 M_{r1} = molecular weight of venlafaxine, 277.40
 M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times V] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times V] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{[C_5 \times V] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point i (mg/mL)
 V = volume of *Medium*, 900 mL
 V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)
 L = label claim (mg/Capsule)
Tolerances: See *Table 5*.

Table 5

Time Point, i	Time (h)	Amount Dissolved
1	2	10%–30%
2	4	35%–55%
3	8	60%–80%
4	12	NLT 70%
5	20	NLT 85%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* <711>.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: Water; 900 mL
Apparatus 1: 100 rpm
Time: 2, 5, 8, and 20 h
Buffer: 11.4 g/L of monobasic ammonium phosphate in water. Adjust with dilute phosphoric acid (1 in 10) or dilute ammonia solution (1 in 10) to a pH of 4.4.
Mobile phase: Acetonitrile and *Buffer* (25.5: 74.5)
Standard solution: ($L/900$) mg/mL of USP Venlafaxine Hydrochloride RS in *Medium*, where L is the label claim, in mg/Capsule
Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. Pass a portion of the withdrawn sample through a suitable filter of 0.45-μm pore size.

Chromatographic system
 (See *Chromatography* <621>, *System Suitability*.)

Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; 5-μm packing L7
Flow rate: 1 mL/min
Injection volume: 10 μL
Run time: 1.5 times the retention time of venlafaxine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
 Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in the *Medium* (mg/mL) after time point i :

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the *Sample solution*
 r_S = peak response from the *Standard solution*
 C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)
 M_{r1} = molecular weight of venlafaxine, 277.40
 M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times V] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times V] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point i (mg/mL)
 V = volume of *Medium*, 900 mL
 V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)
 L = label claim (mg/Capsule)
Tolerances: See *Table 6*.

Table 6

Time Point, i	Time (h)	Amount Dissolved
1	2	NMT 20%
2	5	35%–55%
3	8	60%–80%
4	20	NLT 80%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution <711>.

Test 6: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 6.

Medium: Water; 900 mL, deaerated

Apparatus 1: 100 rpm

Time: 2, 4, 8, 12 and 24 h

Buffer: 10 mL/L of triethylamine in water adjusted with phosphoric acid to a pH of 3.0

Mobile phase: Acetonitrile and Buffer (20:80)

Standard solution: ($L/900$) mg/mL of venlafaxine from USP Venlafaxine Hydrochloride RS in Medium, where L is the label claim, in mg/Capsule

Sample solution: Centrifuge a portion of the solution under test.

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing L1

Flow rate: 2.5 mL/min

Injection volume: 20 μ L

Run time: 1.5 times the retention time of venlafaxine

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in the Medium (mg/mL) after time point i :

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_3)] + [C_1 \times V_3]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - (2 \times V_3))] + [(C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times (V - (3 \times V_3))] + [(C_3 + C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{[C_5 \times (V - (4 \times V_3))] + [(C_4 + C_3 + C_2 + C_1) \times V_3]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in Medium in the portion of sample withdrawn at time point i (mg/mL)

V = volume of Medium, 900 mL

V_3 = volume of the Sample solution withdrawn from the Medium (mL)

L = label claim (mg/Capsule)

Tolerances: See Table 7.

Table 7

Time Point, i	Time (h)	Amount Dissolved
1	2	NMT 30%
2	4	40%–60%
3	8	60%–80%
4	12	70%–90%
5	24	NLT 85%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution <711>.

Test 7: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 7.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 2, 4, 8, 12 and 20 h

Buffer: 1.7 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid (1 in 10) to a pH of 7.0.

Mobile phase: Acetonitrile and Buffer (80:20)

Standard solution: ($L/900$) mg/mL of USP Venlafaxine Hydrochloride RS in Medium, where L is the label claim, in mg/Capsule

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh Medium. Pass a portion of the withdrawn sample through a suitable filter of 0.45- μ m pore size.

Chromatographic system

(See Chromatography <621>, System Suitability.)

Mode: LC

Detector: UV 227 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

Run time: 2 times the retention time of venlafaxine

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in the Medium (mg/mL) after time point i :

$$\text{Result}_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the Sample solution

r_S = peak response from the Standard solution

C_S = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times V] + [C_1 \times V_s]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times V] + [(C_3 + C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

$$\text{Result}_5 = \{[C_5 \times V] + [(C_4 + C_3 + C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

V_s = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See Table 8.

Table 8

Time Point, i	Time (h)	Amount Dissolved
1	2	NMT 10%
2	4	NMT 30%
3	8	40%–70%
4	12	60%–90%
5	20	NLT 80%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to Acceptance Table 2 in *Dissolution* <711>.

Test 8: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 1, 6, 16, and 24 h

Diluent: Acetonitrile and water (30:70)

Buffer: Dissolve 8.9 g of dibasic sodium phosphate dihydrate and 2.5 g of sodium 1-octanesulfonate in 1 L of water. Adjust with 10% phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (32:68)

Standard stock solution: 0.9 mg/mL of USP Venlafaxine Hydrochloride RS prepared as follows. Dissolve the weighed amount of the Standard first in acetonitrile using 20% of flask volume. Sonicate to dissolve, and dilute with *Diluent* to volume.

Standard solution: ($L/900$) mg/mL of USP Venlafaxine Hydrochloride RS from *Standard stock solution* in *Diluent*, where L is the label claim, in mg/Capsule

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. Pass a portion of the withdrawn sample through a suitable filter of 0.45- μ m pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 μ L

Run time: 1.7 times the retention time of venlafaxine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration, C_i , of venlafaxine ($C_{17}H_{27}NO_2$) in the *Medium* (mg/mL) after time point i :

$$\text{Result}_i = (r_u/r_s) \times C_s \times (M_{r1}/M_{r2})$$

r_u = peak response from the *Sample solution*

r_s = peak response from the *Standard solution*

C_s = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point i :

$$\text{Result}_1 = C_i \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times V] + [C_1 \times V_s]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times V] + [(C_3 + C_2 + C_1) \times V_s]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

V_s = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See Table 9.

Table 9

Time Point, i	Time (h)	Amount Dissolved
1	1	NMT 25%
2	6	50%–70%
3	16	70%–95%
4	24	NLT 80%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to Acceptance Table 2 in *Dissolution* <711>. (RB 1-Oct-2012)

- **UNIFORMITY OF DOSAGE UNITS** <905>: Meet the requirements

IMPURITIES

• ORGANIC IMPURITIES

Mobile phase, Standard solution, and Sample solution: Proceed as directed in the *Assay*.

System suitability solution: 0.25 μ g/mL of USP Venlafaxine Related Compound A RS in the *Standard solution*

Chromatographic system(See *Chromatography* ⟨621⟩, *System Suitability*.)**Mode:** LC**Detector:** UV 226 nm**Column:** 4.6-mm × 25-cm; 5-μm packing L1**Flow rate:** 1 mL/min**Injection volume:** 10 μL**Run time:** 4 times the retention time of venlafaxine**System suitability****Sample:** *System suitability solution*

[NOTE—The relative retention times for venlafaxine related compound A and venlafaxine are 0.9 and 1.0, respectively.]

Suitability requirements**Resolution:** NLT 1.5 between venlafaxine related compound A and venlafaxine**Tailing factor:** NMT 2.0 for venlafaxine**Relative standard deviation:** NMT 5.0% for venlafaxine**Analysis****Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

 r_U = peak response of each individual impurity from the *Sample solution* r_S = peak response of venlafaxine from the *Standard solution* C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL) C_U = nominal concentration of venlafaxine in the *Sample solution* (mg/mL) M_{r1} = molecular weight of venlafaxine, 277.40 M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86**Acceptance criteria****Individual impurities:** NMT 0.2%**Total impurities:** NMT 0.5%**ADDITIONAL REQUIREMENTS**

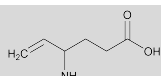
- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:• **USP REFERENCE STANDARDS** ⟨11⟩

USP Venlafaxine Hydrochloride RS

USP Venlafaxine Related Compound A RS

- 1-(1-(4-Methoxyphenyl)-2-(methylamino)ethyl)cyclohexanol hydrochloride.

 $C_{16}H_{25}NO_2 \cdot HCl$ 299.84 • (RB 1-Oct-2012)**Add the following:****•Vigabatrin**

$C_6H_{11}NO_2$ 129.16
 5-Hexenoic acid, 4-amino-;
 4-Amino-5-hexenoic acid [60643-86-9].

DEFINITIONVigabatrin contains NLT 98.0% and NMT 102.0% of vigabatrin ($C_6H_{11}NO_2$), calculated on the anhydrous basis.**IDENTIFICATION**

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the Assay.

ASSAY• **PROCEDURE****Buffer:** 3.4 g/L of monobasic potassium phosphate**Mobile phase:** Acetonitrile, methanol, and *Buffer* (4:40:1000). Adjust with phosphoric acid to a pH of 2.8.**Standard solution:** 2.0 mg/mL of USP Vigabatrin RS in *Mobile phase***System suitability solution:** 12 μg/mL of USP Vigabatrin Related Compound A RS in the *Standard solution***Sample solution:** 2.0 mg/mL of Vigabatrin in *Mobile phase***Chromatographic system**(See *Chromatography* ⟨621⟩, *System Suitability*.)**Mode:** LC**Detector:** UV 210 nm**Column:** 4.6-mm × 25.0-cm; 10-μm packing L9**Flow rate:** 1.5 mL/min**Injection volume:** 20 μL**System suitability****Sample:** *System suitability solution*

[NOTE—The relative retention times for vigabatrin related compound A and vigabatrin are about 0.5 and 1.0, respectively.]

Suitability requirements**Resolution:** NLT 1.5 between vigabatrin related compound A and vigabatrin**Relative standard deviation:** NMT 1.0% for the vigabatrin peak**Analysis****Samples:** *Standard solution* and *Sample solution*Calculate the percentage of vigabatrin ($C_6H_{11}NO_2$) in the portion of Vigabatrin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

 r_U = peak response from the *Sample solution* r_S = peak response from the *Standard solution* C_S = concentration of USP Vigabatrin RS in the *Standard solution* (mg/mL) C_U = concentration of Vigabatrin in the *Sample solution* (mg/mL)**Acceptance criteria:** 98.0%–102.0% on the anhydrous basis**IMPURITIES**

- **HEAVY METALS,** *Method I* ⟨231⟩: NMT 10 μg/g

• **LIMIT OF γ-AMINOBUTYRIC ACID****Solution A:** 1.6 g/L of 9-fluorenylmethyl chloroformate (Fmoc) in acetone**Buffer A:** 4.1 g/L of anhydrous sodium acetate. Adjust with glacial acetic acid to a pH of 4.2.**Buffer B:** 31 g/L of boric acid. Adjust with 0.5 g/mL of sodium hydroxide to a pH of 7.7.**Mobile phase:** Acetonitrile and *Buffer A* (25:75)**Standard stock solution:** 2.0 mg/mL of USP Vigabatrin RS and 4 μg/mL of USP γ-Aminobutyric Acid RS in water**Standard solution:** Transfer 1.0 mL of *Standard stock solution* to a suitable container. Pipet 2 mL of *Buffer B* into the container, and mix. Pipet 3 mL of *Solution A* into the container, mix, and allow to stand for 5 min. Pipet 3 mL of ethyl acetate into the container, shake for a few seconds, and allow the layers to separate. Use the lower layer within 8 h of preparation.**Sample stock solution:** 2.0 mg/mL of Vigabatrin in water

Sample solution: Transfer 1.0 mL of *Sample stock solution* to a suitable container. Pipet 2 mL of *Buffer B* into the container, and mix. Pipet 3 mL of *Solution A* into the container, mix, and allow to stand for 5 min. Pipet 3 mL of ethyl acetate into the container, shake for a few seconds, and allow the layers to separate. Use the lower layer within 8 h of preparation.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 263 nm

Column: 4.6-mm × 15.0-cm; 5-μm packing L11

Flow rate: 1.0 mL/min

Injection volume: 25 μL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for (9-fluorenyl)methanol (FMOH-OH), FMOH-γ-aminobutyric acid, and FMOH-vigabatrin are about 0.4, 0.6, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between FMOH-OH and FMOH-γ-aminobutyric acid

Relative standard deviation: NMT 2.0% for the FMOH-γ-aminobutyric acid peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of γ-aminobutyric acid in the portion of Vigabatrin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of FMOH-γ-aminobutyric acid from the *Sample solution*

r_S = peak response of FMOH-γ-aminobutyric acid from the *Standard solution*

C_S = concentration of USP γ-Aminobutyric Acid RS in the *Standard stock solution* (mg/mL)

C_U = concentration of Vigabatrin in the *Sample stock solution* (mg/mL)

Acceptance criteria

γ-Aminobutyric acid: NMT 0.2%

• ORGANIC IMPURITIES

Buffer: 58.5 g/L of monobasic sodium phosphate in dilute phosphoric acid (23 in 1000)

Mobile phase: Acetonitrile, *Buffer*, and water (25:25:950)

System suitability solution: 6 μg/mL of USP Vigabatrin Related Compound A RS, 7.6 μg/mL of USP Vigabatrin Related Compound B RS, 8 μg/mL of USP Vigabatrin Related Compound E RS, and 4.0 mg/mL of USP Vigabatrin RS in *Mobile phase*

Standard solution: 6 μg/mL of USP Vigabatrin Related Compound A RS, 7.6 μg/mL of USP Vigabatrin Related Compound B RS, and 8 μg/mL of USP Vigabatrin Related Compound E RS in *Mobile phase*

Sample solution: 4.0 mg/mL of Vigabatrin in *Mobile phase*

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 210 nm

Columns: *Column A* and *Column B* are coupled in series before the detector.

Column A: 4.6-mm × 25.0-cm; 5-μm packing L15

Column B: 4.6-mm × 25.0-cm; 10-μm packing L9

Flow rate: 1.0 mL/min

Injection volume: 20 μL

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between vigabatrin related compound A and vigabatrin

Tailing factor: NMT 2.0 each for vigabatrin related compound A and vigabatrin related compound E

Relative standard deviation: NMT 5.0% for vigabatrin related compound E

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of vigabatrin related compound A, vigabatrin related compound B, or vigabatrin related compound E in the portion of Vigabatrin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of vigabatrin related compound A, vigabatrin related compound B, or vigabatrin related compound E from the *Sample solution*

r_S = peak response of vigabatrin related compound A, vigabatrin related compound B, or vigabatrin related compound E from the *Standard solution*

C_S = concentration of USP Vigabatrin Related Compound A RS, USP Vigabatrin Related Compound B RS, or USP Vigabatrin Related Compound E RS in the *Standard solution* (mg/mL)

C_U = concentration of Vigabatrin in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual impurity in the portion of Vigabatrin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of any other individual impurity from the *Sample solution*

r_S = peak response of vigabatrin related compound E from the *Standard solution*

C_S = concentration of USP Vigabatrin Related Compound E RS in the *Standard solution* (mg/mL)

C_U = concentration of Vigabatrin in the *Sample solution* (mg/mL)

Acceptance criteria:

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Vigabatrin related compound E	0.5	0.1
Vigabatrin related compound A	0.9	0.1
Vigabatrin	1.0	—
Vigabatrin related compound B	1.4	0.1
Any other individual impurity	—	0.1
Total impurities ^a	—	0.5

^a Sum of all impurities found in the tests for *Organic Impurities* and *Limit of γ-Aminobutyric Acid*.

• RESIDUE ON IGNITION <281>: NMT 0.1%

SPECIFIC TESTS

• OPTICAL ROTATION, *Specific Rotation* <781>

Sample solution: 200 mg/mL in water. Sonication may be used to aid in dissolution.

Acceptance criteria: +0.5° to −0.5°

• WATER DETERMINATION, *Method I* <921>: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

• USP REFERENCE STANDARDS <11>

USP γ-Aminobutyric Acid RS

4-Aminobutyric acid.

C₄H₉NO₂ 103.12

USP Vigabatrin RS
 USP Vigabatrin Related Compound A RS
 5-Vinylpyrrolidin-2-one.
 C_6H_9NO 111.14
 USP Vigabatrin Related Compound B RS
 (E)-2-(2-Aminoethyl)but-2-enoic acid hydrochloride.
 $C_6H_{11}NO_2 \cdot HCl$ 165.62
 USP Vigabatrin Related Compound E RS
 2-(2-Aminobut-3-enyl)malonic acid.
 $C_7H_{11}NO_4$ 173.17 ■1S (USP36)

Sterile Purified Water

[NOTE—For microbiological guidance, see *Water for Pharmaceutical Purposes* (1231).]

H₂O 18.02

DEFINITION

Sterile Purified Water is Purified Water sterilized and suitably packaged. It contains no antimicrobial agents. [NOTE—Do not use Sterile Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection.]

SPECIFIC TESTS

Change to read:

• OXIDIZABLE SUBSTANCES

Sample: 100 mL

Analysis: Add 10 mL of 2 N sulfuric acid, and heat to a boil. For Sterile Purified Water in containers having a fill volume of less than 50 mL, add 0.4 mL of 0.02 M potassium permanganate, and boil for 5 min; where the fill volume is 50 mL or more, add 0.2 mL of 0.02 M potassium permanganate, and boil for 5 min. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter.

Acceptance criteria: The pink color does not completely disappear. ■Alternatively, perform the test for *Total Organic Carbon* (643), *Sterile Water*. ■1S (USP36)

Add the following:

- **TOTAL ORGANIC CARBON**, *Sterile Water* (643): Meets the requirements. Alternatively, perform the test for *Oxidizable Substances*. ■1S (USP36)
- **WATER CONDUCTIVITY**, *Sterile Water* (645): Meets the requirements
- **STERILITY TESTS** (71): Meets the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE**: Preserve in suitable tight containers.
- **LABELING**: Label it to indicate the method for preparation and to indicate that it is not for parenteral administration.

Sterile Water for Inhalation

[NOTE—For microbiological guidance, see *Water for Pharmaceutical Purposes* (1231).]

DEFINITION

Sterile Water for Inhalation is prepared from Water for Injection that is sterilized and suitably packaged. It contains no

added antimicrobial agents. [NOTE—Do not use Sterile Water for Inhalation for parenteral administration or for other sterile compendial dosage forms.]

SPECIFIC TESTS

Change to read:

• OXIDIZABLE SUBSTANCES

Sample: 100 mL

Analysis: Add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Inhalation in containers having a fill volume of less than 50 mL, add 0.4 mL of 0.02 M potassium permanganate, and boil for 5 min; where the fill volume is 50 mL or more, add 0.2 mL of 0.02 M potassium permanganate, and boil for 5 min. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter.

Acceptance criteria: The pink color does not completely disappear. ■Alternatively, perform the test for *Total Organic Carbon* (643), *Sterile Water*. ■1S (USP36)

Add the following:

- **TOTAL ORGANIC CARBON**, *Sterile Water* (643): Meets the requirements. Alternatively, perform the test for *Oxidizable Substances*. ■1S (USP36)
- **WATER CONDUCTIVITY**, *Sterile Water* (645): Meets the requirements
- **STERILITY TESTS** (71): Meets the requirements
- **BACTERIAL ENDOTOXINS TEST** (85): Less than 0.5 USP Endotoxin Unit/mL

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE**: Preserve in glass or plastic containers. Glass containers are preferably of Type I or Type II glass.
- **LABELING**: Label it to indicate that it is for inhalation therapy only and that it is not for parenteral administration.
- **USP REFERENCE STANDARDS** (11)
USP Endotoxin RS

Sterile Water for Injection

[NOTE—For microbiological guidance, see *Water for Pharmaceutical Purposes* (1231).]

DEFINITION

Sterile Water for Injection is prepared from Water for Injection that is sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

SPECIFIC TESTS

Change to read:

• OXIDIZABLE SUBSTANCES

Sample: 100 mL

Analysis: Add 10 mL of 2 N sulfuric acid, and heat to a boil. For Sterile Water for Injection in containers having a fill volume less than 50 mL, add 0.4 mL of 0.02 M potassium permanganate, and boil for 5 min; where the fill volume is 50 mL or more, add 0.2 mL of 0.02 M potassium permanganate, and boil for 5 min. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter.

Acceptance criteria: The pink color does not completely disappear. ■Alternatively, perform the test for *Total Organic Carbon* (643), *Sterile Water*. ■1S (USP36)

Add the following:

- **TOTAL ORGANIC CARBON**, *Sterile Water* <643>: Meets the requirements. Alternatively, perform the test for *Oxidizable Substances*.■1S (USP36)
- **WATER CONDUCTIVITY**, *Sterile Water* <645>: Meets the requirements
- **PARTICULATE MATTER IN INJECTIONS** <788>: Meets the requirements
- **STERILITY TESTS** <71>: Meets the requirements
- **BACTERIAL ENDOTOXINS TEST** <85>: Less than 0.25 USP Endotoxin Unit/mL

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE**: Preserve in single-dose glass or plastic containers of not larger than 1-L size. Glass containers are preferably of Type I or Type II glass.
- **LABELING**: Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute.
- **USP REFERENCE STANDARDS** <11>
USP Endotoxin RS

Sterile Water for Irrigation

[NOTE—For microbiological guidance, see *Water for Pharmaceutical Purposes* <1231>.]

DEFINITION

Sterile Water for Irrigation is prepared from Water for Injection that is sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

SPECIFIC TESTS**Change to read:**• **OXIDIZABLE SUBSTANCES**

Sample: 100 mL

Analysis: Add 10 mL of 2 N sulfuric acid, and heat to a boil. For Sterile Water for Irrigation in containers having

a fill volume less than 50 mL, add 0.4 mL of 0.02 M potassium permanganate, and boil for 5 min; where the fill volume is 50 mL or more, add 0.2 mL of 0.02 M potassium permanganate, and boil for 5 min. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter.

Acceptance criteria: The pink color does not completely disappear. ■Alternatively, perform the test for *Total Organic Carbon* <643>, *Sterile Water*.■1S (USP36)

Add the following:

- **TOTAL ORGANIC CARBON**, *Sterile Water* <643>: Meets the requirements. Alternatively, perform the test for *Oxidizable Substances*.■1S (USP36)
- **WATER CONDUCTIVITY**, *Sterile Water* <645>: Meets the requirements
- **STERILITY TESTS** <71>: Meets the requirements
- **BACTERIAL ENDOTOXINS TEST** <85>: Less than 0.25 USP Endotoxin Unit/mL

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE**: Preserve in single-dose glass or plastic containers. Glass containers are preferably of Type I or Type II glass. The container may contain a volume of more than 1 L and may be designed to empty rapidly.
- **LABELING**: Label it to indicate that no antimicrobial or other substance has been added. The designations “For irrigation only” and “Not for injection” appear prominently on the label.
- **USP REFERENCE STANDARDS** <11>
USP Endotoxin RS

Combined Index to USP 36 and NF 31, including First Supplement

Page citations refer to the pages of Volumes 1, 2, and 3 of USP 36–NF 31 and its First Supplement.

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